# *A COMPARATIVE STUDY OF EFFICACY, SIDE EFFECTSAND THEIR MANAGEMENT OF NAPROXEN AND FLUPIRTINE IN CANCER PATIENTS.*

***Dissertation submitted in partial fulfillment of the requirement for the award of the degree of***

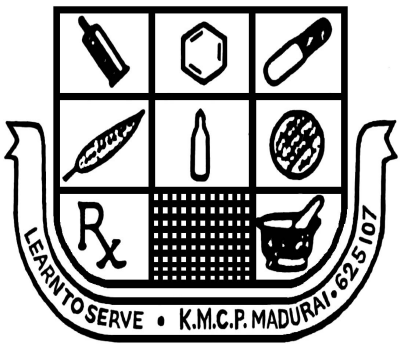
**MASTER OF PHARMACY**

**IN**

**PHARMACY PRACTICE**

**THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY,**

**CHENNAI**

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# CERTIFICATE

This is to certify that the dissertation entitled **"A COMPARATIVE STUDY OF EFFICACY, SIDE EFFECTS AND THEIR MANAGEMENT OF NAPROXEN AND FLUPIRTINE IN CANCER PATIENTS"** submitted by **Ms. RENITA KALPANA ROY**, to The Tamilnadu Dr. M.G.R Medical university, Chennai**,** in partial fulfillment of the requirement for the award of **Master of Pharmacy in Pharmacy Practice**, at **K.M.College of Pharmacy,** Uthangudi, Madurai-107, is a bonafide work carried out by her under my guidance and supervision during the academic year of 2013 – 2014. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other universities.

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This is to certify that the dissertation entitled "**A COMPARATIVE STUDY OF EFFICACY, SIDE EFFECTS AND THEIR MANAGEMENT OF NAPROXEN AND FLUPIRTINE IN CANCER PATIENTS"** is a bonafide work done by "**Ms.Renita Kalpana Roy, Reg. No. 261240057** at **K.M College Of Pharmacy, Madurai"** in partial fulfilment of the university rules and regulations for award of **Master Of Pharmacy**, under my guidance and supervision during the academic year 2013 – 2014.

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# ABBREVIATIONS

| | | |
|---|---|---|
| **CA** | **-** | Cancer |
| **CVD** | - | Cardiovascular Disease |
| **CAD** | **-** | Coronary Artery Disease |
| **LDL** | - | Low Density Lipoprotein |
| **HDL** | - | High Density Lipoprotein |
| **TC** | - | Total Cholesterol |
| **TG** | - | Triglycerides |
| **VLDL** | - | Very Low Density Lipoprotein |
| **IDL** | - | Intermediate Density Lipoprotein |
| **NCEP** | - | National Cholesterol Education Program |
| **Lp (a)** | - | Lipoprotein |
| **ATP** | - | Adult Treatment Panel |
| **CE** | - | Cholesteryl Ester |
| **PVD** | - | Peripheral Vascular Disease |
| **Apo** | - | Apolipoprotein |
| **CHD** | - | Coronary Heart Disease |
| **HMG-CoA** | - | Hydroxy-3-Methylglutaryl coenzyme A |
| **MI** | - | Myocardial Infarction |
| **LPL** | - | Lipoprotein Lipase |
| **LCAT** | - | Lecithin Cholesterol Acyl Transferase |
| **AST** | - | Aspartate Aminotransferase |
| **ALT** | - | Alanine Aminotransferase |
| **GGT** | - | Gamma-Glutamyl Transferase |
| **PTCA** | - | Percutaneous Transluminal Coronary Angioplasty |

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# INTRODUCTIONS

Cancer is a class of diseases characterized by out-of-control cell growth[1] . The cells grow and divide without space without respect to limits(aggressive), invade and destroy adjacent tissues(invasive), and spread to others locations in the body(metastatic). These three malignant properties of cancers differentiate them from benign tumors, which are self-limited in their growth and do not invade or metastasize (spread or grow).

All cancers are caused by abnormalities in genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiations, chemicals or infectious agents. Cancers cause about 13% of all death.

Carcinogens are a class of substances that are directly responsible for damaging DNA, promoting or aiding cancer[2]. Tobacco, asbestos, arsenic, radiation such as gamma and x-rays, the sun, and compounds in car exhaust fumes are all examples of carcinogens. When our bodies are exposed to carcinogens, free radicals are formed that try to steal electrons from other molecules in the body. Theses free radicals damage cells and affect their ability to function normally. Cancer can be the result of a genetic predisposition that is inherited from family members. It is possible to be born with certain genetic mutations or a fault in a gene that makes one statistically more likely to develop cancer later in life. As the age increases , there is an increase in the number of possible cancer-causing mutations in the DNA. This makes age an important risk factor for cancer. Several viruses have also been linked to cancer such as: human papilloma virus (a cause of cervical cancer), hepatitis B and C (causes of liver cancer), and Epstein-Barr virus (a cause of some childhood cancers).

Human immunodeficiency virus (HIV) - and anything else that suppresses or

weakens the immune system - inhibits the body's ability to fight infections and increases the chance of developing cancer

Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors (except in the case of leukemia where cancer prohibits normal blood function by abnormal cell division in the blood stream). Tumors can grow and interfere with the digestive, nervous, and circulatory systems and they can release hormones that alter body function. Tumors that stay in one spot and demonstrate limited growth are generally considered to be benign.

Cancer promoting oncogens are often activated in cancer cells, giving those cells new properties, such as hyperactive growth and divisions, protection against programmed cell death, loss of respect for normal tissue boundaries, and ability to become established in diverse tissue environments. Tumor suppressor genes are often inactivated in cancer cells, resulting in loss of normal functions in those cells, such as accurate DNA replications, control over the cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system.

A definitive diagnosis usually requires the histologic examination of a tissue biopsy specimen by a pathologist, although the initial indication of malignancy can be symptoms or radiography imaging abnormalities. Most cancers can be treated and some cured, depending on the specific type, location and stage. Once diagnosed cancer is usually treated with a combination of surgery, chemotherapy and radiotherapy.

## CANCER BIOLOGY:

The Cancer Biology portion of the site contains in depth information about the structure and function of normal cells and cancer cells. The changes that make

normal cells turn into cancer cells are described. Cancer systems biology encompasses the application of systems biology approaches to cancer research, in order to study the disease as a complex adaptive system with emerging properties at multiple biological scales[3]. More explicitly, becausecancer spans multiple biological, spatial and temporal scales, communication and feedback mechanisms across the scales create a highly complex dynamic system. The relationships between scales is not simple or necessarily direct, and sometimes become combinatorial, so that systems approaches are essential to evaluate these relationships quantitatively and qualitatively.

Cancer systems biology therefore adopts a holistic view of cancer[4]. aimed at integrating its many biological scales, including genetics, signaling networks[5], epigenetics[6], cellular behavior, histology, (pre)clinical manifestations and epidemiology. Ultimately, cancer properties at one scale, e.g., histology, are explained by properties at a scale below, e.g., cell behavior. Likewise, a higher scale, e.g., epidemiology, can encroach on a lower scale, e.g., genetics. The fundamental concept is that percolation of properties across scales must be measured and taken into account in order to fully understand etiology, progression and dynamics of cancer.

The systems biology approach relies heavily on the successes of decades of reductionism, which has clarified the component parts and mechanistic principles of living organisms, as well as their key alterations in cancer, especially at the genetic/genomic scale, to deep detail. Basic researchers and clinicians have progressively recognized the complexity of cancer and of its interaction with the micro- and macro-environment, since putting together the components to provide a cohesive view of the disease has been challenging and hampered progress. Cancer Systems Biology transcends the “reductionist” approach to cancer that typically

produces causative explanations focused on a single gene or mutation, with little emphasis on inter-scale relationships.

## Biological Building Blocks:

Humans are made up of many millions of cells. In order to understand what goes wrong in cancer, it is important to understand normal cells work. The first step is to discuss the structure and basic functions of cells. All living things, including the cells that make up a human body are comprised of a small subset of different biomolecules. There are four main classes,

- Carbohydrates
- Proteins
- Lipids
- Nucleic Acids

Additional biomolecules can be made by combining these four types. As an example, many proteins are modified by the addition of carbohydrate chains. The end product is called a glycoprotein.

## Cells and Cell Structure:

The tiny cells that make up these organs actually contain within them smaller structures called organelles. Organelles are identified by microscopy, and can also be purified by cell fractionation. There are many types of organelles, particularly in eukaryotic cells. While prokaryotes do not possess organelles per se, some do contain protein-based microcompartments, which are thought to act as primitive organelles[7]. These organelles help the cells to perform their jobs. In cancer, changes to these organelles can cause the individual cells and ultimately the entire organism to have serious problems.

## Cell Division and Mitosis:

During a lifetime, many of the cells that make up the body age and die. These cells must be replaced so that the body can continue functioning optimally the reasons include the following:

- Sloughing off of epithelial cells such as those lining the skin and intestines. The old, worn out cells on the surface of the tissues are constantly replaced. A special case of this is the monthly replacement of the cells lining the uterus in pre-menopausal women.
- Wound healing requires that cells in the area of the damage multiply to replace those lost. Viral diseases such as hepatitis may also cause damage to organs that then need to replace lost cells.
- Replacement of the cells that make up blood. Red blood cells carry oxygen to tissues. White blood cells such as B and T lymphocytes are part of the body's immune system and help to ward off infections. Most of these cells have very short lifespans and must be constantly replaced. The precursors of these cells are located in bone marrow. These precursors, or stem cells, must reproduce at a very high rate to maintain adequate amounts of the blood cells. The process by which a cell reproduces to create two identical copies of itself is known as mitosis. The goal of mitosis is the formation of two identical cells from a single parent cell. The cells formed are known as daughter cells.

In order for this to happen, the following must occur:

- The genetic material, the DNA in chromosomes, must be faithfully copied. This occurs via a process known as replication.
- The organelles, such as mitochondria, must be distributed so that each daughter cell receives an adequate amount to function.
- The cytoplasm of the cell must be physically separated into two different cells.

Many of the features of cancer cells are due to defects in the genes that control cell division. The cell division process occurs as an orderly progression through four different stages. These four stages are collectively known as the cell cycle.

## Gene Function:

The chromosomes within our cells contain an enormous amount of information. It is estimated that humans have somewhere around 30,000 genes. Each gene codes for an RNA molecule that is either used directly or used as a guide for the formation of a protein such as the insulin shown earlier. Information in our cells generally flows in a predictable order from the storage form of the information (DNA) through the working form (RNA) into the final product (protein). DNA is used as a guide or template for the production of more DNA. This process, known as replication, is addressed in the section on cell division. The process in which particular sections of DNA (genes) are used to produce RNA is known as transcription. We will cover transcription in some detail because alterations in the transcription of certain genes are very important in the development of cancer. The set of genes that are 'on' at any given time is critical. The variable environment in which we live means that different genes need to be 'on' at different times. For example, if a meal contains large amounts of lactose, a sugar found in milk, then our bodies respond by turning on (transcribing) the genes that lead to the production of enzymes that break down lactose. If a different sugar or nutrient is present, the correct genes need to be turned on to process it.

## Mutation:

Cancer is a result of the breakdown of the controls that regulate cells. The causes of the the breakdown always include changes in important genes. The changes are often the result of mutations, changes in the DNA sequence of

chromosomes. Mutations can be very small changes, affecting only a few nucleotides or they can be very large, leading to major changes in the structure of chromosomes. Due to the damaging effects that mutations can have on genes, organisms have mechanisms such as DNA repair to prevent or correct (revert the mutated sequence back to its original state) mutations[8].

Both small and large mutations can affect the behavior of cells. Combinations of mutations in important genes can lead to the development of cancer. The material covered in these sections describes the relationship between mutation and cancer, the different kinds of mutations and what causes them.

## Cancer Genes:

The cell division process is dependent on a tightly controlled sequence of events. These events are dependent on the proper levels of transcription and translation of certain genes. When this process does not occur properly, unregulated cell growth may be the end result. Of the 30,000 or so genes that are currently thought to exist in the human genome, there is a small subset that seems to be particularly important in the prevention, development, and progression of cancer. These genes have been found to be either malfunctioning or non-functioning in many different kinds of cancer.The genes that have been identified to date have been categorized into two broad categories, depending on their normal functions in the cell. Genes whose protein products stimulate or enhance the division and viability of cells.

This first category also includes genes that contribute to tumor growth by inhibiting cell death. Genes whose protein products can directly or indirectly prevent cell division or lead to cell death.The normal versions of genes in the first group are called proto-oncogenes. The mutated or otherwise damaged versions of these genes are called oncogenes.

**Cancer Formation:**

Cancer is the result of unregulated cell division. Cancer cells divide when they are not supposed to, don't stop dividing when they are supposed to and don't die when they should. In the worst cases, the cancer cells leave the area in which they arose and travel to other parts of the body.

In cancer cells, changes to key genes cause the cells to act abnormally. The changes are often the result of changes to the DNA (mutations) in the cells. Because there are many different things that are capable of causing mutation, there are an equally large number of causes of cancer.

The development of cancer takes place in a multi-step process. As the cells become more abnormal, they gain new capabilities, such as the ability to release growth factors and digestive enzymes. The cells continue to divide, impacting nearby normal cells, often reducing the function of the affected organ. Even abnormal cancer cells die sometime and a tumor that is large enough to feel can take years to reach that size. Although not all cancers share exactly the same steps, there are some general features that are shared in the development of many types of cancer. Another critical step in the growth of a tumor is the development of a blood supply (angiogenesis). Blood provides nutrients, carries away waste and the blood vessels provide a way for cancer cells to move around the body.

**Angiogenesis:**

Angiogenesis is the physiological process through which new blood vessels form from pre-existing vessels. This is distinct from vasculogenesis, which is the de novo formation of endothelial cells from mesoderm cell precursors[9].The first vessels in the developing embryo form through vasculogenesis, after which angiogenesis is responsible for most, if not all, blood vessel growth during development and in disease[10].

All cells need a constant source of oxygen and nutrients such as glucose (sugar). Our cells get their nutrients delivered to them via the blood. Nutrients and oxygen are pumped through the body via the circulatory system. Once in the tissues, the nutrients cross the blood vessel walls and enter the spaces around the cells.

Cells need nutrients constantly, and the process by which nutrients float over to cells takes time. In order to make sure that all cells get enough nutrients, our tissues are full of many small blood vessels (capillaries) that can deliver food to within a very short distance of any cell.Even though cancer cells are abnormal, they still require oxygen and nutrients. The development of blood vessels is an essential step in the growth of a tumor. Without vessels tumors cannot grow to be larger than a small fraction of an inch .When the area around the cells in a tumor starts to get too far from a blood vessel, the oxygen and nutrient levels start to go down. A decrease in oxygen is also called hypoxia. Hypoxia triggers changes in the behavior of the tumor cells.The tumor cells produce (or cause nearby cells to produce) growth factors that stimulate the formation of blood vessels. Tumors that do not produce (or cause other cells to produce) angiogenesis factors cannot grow. One of the most well-studied angiogenesis factors is called vascular endothelial derived growth factor (VEGF). VEGF or other angiogenesis factors produced by tumor cells or nearby cells can cause the development of blood vessels that feed the growing tumor. Because VEGF is a normal signal for the cells forming the blood vessels, they are really just doing their job.

The tumor 'tricks' the body into creating new blood vessels. The blood vessels created in this way are not exactly the same as normal blood vessels. Frequently they are less organized and leakier than normal vessels.

Abnormal angiogenesis is not limited to cancer. Other diseases, including macular degeneration, a progressive eye disease, are linked to abnormal development of blood vessels.

**Metastasis:**

Metastasis is responsible for the great majority of deaths in cancer patients. It is the spread of a cancer from one organ or part to another non-adjacent organ or part. The new occurrences of disease thus generated are referred to as metastases[11]. Metastasis is the process by which cancer cells migrate throughout the body. In order for cells to move through the body, they must first climb over/around neighboring cells. They do this by rearranging their cytoskeleton and attaching to the other cells and the extracellular matrix via proteins on the outside of their plasma membranes. By extending part of the cell forward and letting go at the back end, the cells can migrate forward. The cells can crawl until they hit a blockage which cannot be bypassed. Often this block is a thick layer of proteins and glycoproteins surrounding the tissues, called the basal lamina or basement membrane. In order to cross this layer, cancer cells secrete a mixture of digestive enzymes that degrade the proteins in the basal lamina and allow them to crawl through.The proteins secreted by cancer cells contain a group of enzymes called matrix metalloproteases (MMP). These enzymes act as 'molecular scissors' to cut through the proteins that inhibit the movement of the migrating cancer cells. Once the cells have traversed the basal lamina, they can spread through the body in several ways. They can enter the bloodstream by squeezing between the cells that make up the blood vessels. Once in the blood stream, the cells float through the circulatory system until they find a suitable location to settle and re-enter the tissues. The cells can then begin to grow in this new location, forming a new tumor. The process of metastasis formation is very inefficient process but leads to

the majority of deaths associated with cancer. This is because the number of cells that leave a tumor can be in the millions per day.

Even if only a small fraction of the cells that leave a tumor are able to survive to form a new tumor, the large number of attempts means that a distant growth is likely to occur at some point Migrating cancer cells can die from a variety of causes.

The causes includes:

- Cells normally live tightly connected to their neighbors and the meshwork of proteins surrounding them. Detachment from the surface of other cells can lead to cell death.
- Cancer cells are often quite large in comparison to the cells that normally live in the lymphatic system or blood system. When they travel through the vessels they can get damaged or stuck, leading to cell death.
- Cancer cells can be recognized and destroyed by cells of the immune system

Additionally, it is important to note that even if a cancer cell does not die, it does not mean that it will form a tumor. The cells may exist at locations far from the original tumor without multiplying enough to cause any problems.

**Tumor-Host Interactions[12]:**

Tumors are surrounded by resident non-cancerous cells, connective tissue, and extracellular matrix. These components are known as the tumor stroma or microenvironment. Within the past several years, it has become evident that the tumor microenvironment plays an important role in both tumor initiation and progression. Due to this new knowledge, researchers have begun to investigate treatments that target both the cancer and its surroundings.

**Immune System:**

The immune system consists of a large number of different types of cells and proteins that function to distinguish between normal and abnormal cellular components and between 'self' and 'non-self'. As an example, when a thorn gets stuck in the body, the immune cells are able to recognized the thorn as a foreign object (i.e. 'non-self') and attack it. The same is true for bacteria, viruses or other organisms that can invade our bodies. More subtle distinction between self and non-self occurs in the recognition of cancer cells by the forces of the immune system. The cancer cells are recognized and attacked because they differ from the normal 'self' from which they arose. The main cells of the specific immune response are lymphocytes - B cells and T cells. All lymphocyte precursors originate in the bone marrow. The pre-B cells stay in the bone marrow to undergo further development, while the T cell precursors migrate to an immune organ located in the neck (the thymus) to further develop. In fact, T cells get their name from the thymus. For trivia buffs: B cells are named after an organ found in chickens (the bursa of Fabricius) where they were first studied. Humans do not have an equivalent organ.Early in T cell and B cell development, developing cells that strongly react with normal cell proteins are removed from the system. In this way, the immune system ensures that the B cells and T cells do not kill normal body cells. If self-reactive T cells and B cells are not removed from the lymphocyte population, autoimmune diseases like lupus or rheumatoid arthritis may develop.

There are two classes of mature T cells:

- Helper T cells- These cells help other immune cells, including CTLs, macrophages and B cells, carry out their functions more efficiently.
- Cytotoxic T Lymphocytes (CTL)-(cyto=cell and toxic because they can kill) These are cells that are able to kill other cells, they are cellular assasins. They directly kill any cell that they recognize as abnormal, such as cells infected with viruses or cancer cells.

The immature T cells residing in the lymph nodes and spleen do not mature into full effectors cells until an APC comes to them and shows them, or presents to them, a particular protein antigen. Once the T cell is notified by the APC that there are cells in the body expressing these abnormal proteins, the T cells mature and leave the lymph nodes and the spleen to circulate in the body and find the abnormal cells. When the T cells find the abnormal cells they are able to kill them. In the case of virus infection, killing the infected cell is a harsh but effective way to limit the production of the viruses within. Cancer cells may also be recognized and eliminated by cytotoxic cells of the immune system.

B cells are another critical component of the acquired immune response. Like T cells, B cells are formed in the bone marrow. The cells move out into the body to mature. B cells are responsible for producing antibodies, proteins that recognize foreign objects that enter the body (viruses, bacteria, other proteins, etc.).

B cells can recognize different targets.There are millions of different kinds of B cells in our bodies and our immune system can respond to a very large number of different 'foreign' targets.The immune system functions as an effective surveillance system to eliminate abnormal cells and invading organisms from our bodies.

**PROGNOSIS:**

Cancer has a reputation as a deadly disease. Taken as a whole, about half of people receiving treatment for invasive cancer (excluding carcinoma in situ and non-melanoma skin cancers) die from cancer or its treatment[13]. Survival is worse in the developing world . However, the survival rates vary dramatically by type of

cancer, with the range running from basically all people surviving to almost no one surviving.

Those who survive cancer are at increased risk of developing a second primary cancer at about twice the rate of those never diagnosed with cancer[14]. The increased risk is believed to be primarily due to the same risk factors that produced the first cancer, partly due to the treatment for the first cancer, and potentially related to better compliance with screening.

Predicting either short-term or long-term survival is difficult and depends on many factors. The most important factors are the particular kind of cancer and the patient's age and overall health. People who are frail with many other health problems have lower survival rates than otherwise healthy people. A centenarian is unlikely to survive for five years even if the treatment is successful. People who report a higher quality of life tend to survive longer[15].

People with lower quality of life may be affected by major depressive disorder and other complications from cancer treatment and/or disease progression that both impairs their quality of life and reduces their quantity of life. Additionally, patients with worse prognoses may be depressed or report a lower quality of life directly because they correctly perceive that their condition is likely to be fatal.

**EPIDEMIOLOGY:**

In U.S and other developed countries, cancer is presently responsible for about 20 %of all death. On the yearly basis, 0.9% of the population is diagnosed with cancer. In 2008, it was estimated that there are just over two million people living with or beyond cancer in the UK who had previously been diagnosed, and this is predicted to rise by more than 3% a year. Prevalence figures are influenced by both incidence and survival. Thus, the most prevalent types of cancer are those with a relatively high incidence rate and a good prognosis. In the UK the most

prevalent cancer in males is prostate cancer and in females it is breast cancer. The latest analysis shows that at the end of 2006, there were over 200,000 prevalent cancer patients in the UK who were alive one year after their diagnosis. In total, there were 1.13 million cancer survivors in the UK who were alive up to 10 years from diagnosis at the end of 2006.

These latest estimates are much higher than previous forecasts of cancer prevalence because incidence has been rising whilst the death rates have continued to fall, leading to better survival. This is expected to continue over the coming years as a result of a number of factors, including an ageing population, earlier detection of cancer and continued improvements in treatment. In India, the number of new breast cancer cases is about 115,000 per year and this is expected to rise to 250,000 new cases per year by 2015. Some slow-growing cancers are particularly common. Autopsy studies in Europe and Asia have shown that up to 36% of people have undiagnosed and apparently harmless thyroid cancer at the time of their deaths, and that 80% of men develop prostate cancer by age 80. As these cancers did not cause the person's death, identifying them would have represented over diagnosis rather than useful medical care. The three most common childhood cancers are leukemia (34%), brain tumors (23%), and lymphomas (12%)[16]. Rates of childhood cancer have increased by 0.6% per year between 1975 to 2002 in the United States[17] .

**CLASSIFICATION:**

Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The specific factors used to determine tumor grade vary with each type of cancer. Histologic grade, also called differentiation, refers to how much the tumor cells resemble normal cells of the

same tissue type. Nuclear grade refers to the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are dividing. Tumor grade should not be confused with the stage of a cancer. Cancer stage refers to the extent or severity of the cancer, based on factors such as the location of the primary tumor, tumor size, number of tumors, and lymph node involvement (spread of cancer into lymph nodes). If a tumor is suspected to be malignant, a sample of tissue or the entire tumor in a procedure called a biopsy and is the tissue is examined to determine whether the tumor is benign or malignant. Based on the microscopic appearance of cancer cells, it is commonly described tumor grade by four degrees of severity: Grades 1, 2, 3, and 4. The cells of Grade 1 tumors resemble normal cells, and tend to grow and multiply slowly. Grade 1 tumors are generally considered the least aggressive in behavior. Conversely, the cells of Grade 3 or Grade 4 tumors do not look like normal cells of the same type. Grade 3 and 4 tumors tend to grow rapidly and spread faster than tumors with a lower grade. Grading systems are different for each type of cancer. For example, pathologists use the Gleason system to describe the degree of differentiation of prostate cancer cells. The Gleason system uses scores ranging from Grade 2 to Grade 10. Lower Gleason scores describe well-differentiated, less aggressive tumors. Higher scores describe poorly differentiated, more aggressive tumors. Other grading systems include the Bloom-Richardson system for breast cancer and the Fuhrman system for kidney cancer. Use tumor grade and many other factors, such as cancer stage, to develop an individual treatment plan for the patient and to predict the patient's prognosis. Generally, a lower grade indicates a better prognosis (the likely outcome or course of a disease; the chance of recovery or recurrence).

However, the importance of tumor grade in planning treatment and estimating a patient's prognosis is greater for certain types of cancers, such as soft tissue sarcoma, primary brain tumors, lymphomas, and breast and prostate cancer.

Patients should speak with their doctor about tumor grade and how it relates to their diagnosis and treatment.

Cancers are classified by the type of cell that the tumor cells resemble and is therefore presumed to be the origin of the tumor.

These types include:

**Carcinomas**: malignant tumor derived from cells (epithelial cells) that cover internal and external parts of the body. Eg. common cancers including lung, prostrate, breast, and colon cancer

**Sarcomas:** malignant tumor derived from cells that are located in bone, cartilage, fat, connective tissue, muscle, and other supportive tissues.

**Lymphomas** are cancers that begin in the lymph nodes and immune system tissues[19].

**Leukemias** are cancers that begin in the bone marrow and often accumulate in the bloodstream[19].

**Germ cell tumor:** tumors derived from totipotent cells. In adults most often found in testicles and ovary; in fetuses, babies and children mostly often found on the body midline.

**Adenomas** are cancers that arise in the thyroid, the pituitary gland, the adrenal gland, and other glandular tissues.

**Blastic tumor:** A tumor which resembles an immature embryonic

**CAUSES OF CANCER:**

Cancers are primarily an environmental disease with 90–95% of cases attributed to environmental factors and 5–10% due to genetics. Environmental, as used by cancer researchers, means any cause that is not inherited genetically, not merely pollution[20]. Common environmental factors that contribute to cancer death include tobacco (25–30%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental

pollutants. It is nearly impossible to prove what caused a cancer in any individual, because most cancers have multiple possible causes.

For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, then there is a small chance that the cancer developed because of air pollution or radiation[21].

**Chemicals:**

Cancer pathogenesis is traceable back to DNA mutations that impact cell growth and metastasis. Substances that cause DNA mutations are known as mutagens, and mutagens that cause cancers are known as carcinogens. Particular substances have been linked to specific types of cancer.Tobacco smoking is associated with many forms of cancer, and causes 90% of lung cancer[22]. Many mutagens are also carcinogens, but some carcinogens are not mutagens. Alcohol is an example of a chemical carcinogen that is not a mutagen[23].Cancer related to one's occupation is believed to represent between 2–20% of all cases[24]. Every year, at least 200,000 people die worldwide from cancer related to their workplace[25]. Most cancer deaths caused by occupational risk factors occur in the developed world. It is estimated that approximately 20,000 cancer deaths and 40,000 new cases of cancer each year in the U.S. are attributable to occupation[26]. Millions of workers run the risk of developing cancers such as lung cancer and mesothelioma from inhaling asbestos fibers and tobacco smoke, or leukemia from exposure to benzene at their workplaces.

**Diet and exercise:**

Diet, physical inactivity, and obesity are related to approximately 30–35% of cancer deaths[27]. In the United States excess body weight is associated with the development of many types of cancer and is a factor in 14–20% of all cancer

deaths. Physical inactivity is believed to contribute to cancer risk not only through its effect on body weight but also through negative effects onimmune system and endocrine system. More than half of the effect from diet is due to overnutrition rather than from eating too little healthy foods. Diets that are low in vegetables, fruits and whole grains, and high in processed or red meats are linked with a number of cancers. A high-salt diet is linked to gastric cancer, aflatoxin B1, a frequent food contaminate, with liver cancer, and Betel nut chewing with oral cancer[28]. This may partly explain differences in cancer incidence in different countries. For example, gastric cancer is more common in Japan due to its high-salt diet[29] and colon cancer is more common in the United States. Immigrants develop the risk of their new country, often within one generation, suggesting a substantial link between diet and cancer[30].

**Infection:**

Worldwide approximately 18% of cancer deaths are related to infectious diseases[31]. This proportion varies in different regions of the world from a high of 25% in Africa to less than 10% in the developed world. Viruses are the usual infectious agents that cause cancer but bacteria and parasites may also have an effect. A virus that can cause cancer is called an oncovirus. These include human papillomavirus (cervical carcinoma), Kaposi's sarcoma herpesvirus (Kaposi's sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1(T-cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma[32]. Parasitic infections strongly associated with cancer include Schistosoma haematobium (squamous cell carcinoma of the bladder) and the liver flukes, Opisthorchis viverrini and Clonorchis sinensis (cholangiocarcinoma).

**Radiation:**

Up to 10% of invasive cancers are related to radiation exposure, including both ionizing radiation and non-ionizing ultraviolet radiation[33]. Additionally, the vast majority of non-invasive cancers are non-melanoma skin cancers caused by non-ionizing ultraviolet radiation. Sources of ionizing radiation include medical imaging, and radon gas. Radiation can cause cancer in most parts of the body, in all animals, and at any age, although radiation-induced solid tumors usually take 10–15 years, and can take up to 40 years, to become clinically manifest, and radiation-induced leukemias typically require 2–10 years to appear[34]. Some people, those with nevoid basal cell carcinoma syndrome or retinoblastoma, are more susceptible than average to developing cancer from radiation exposure. Children and adolescents are twice as likely to develop radiation-induced leukemia as adults; radiation exposure before birth has ten times the effect. Ionizing radiation is not a particularly strong mutagen. Residential exposure to radon gas, for example, has similar cancer risks as passive smoking. Low-dose exposures, such as living near a nuclear power plant, are generally believed to have no or very little effect on cancer development. Radiation is a more potent source of cancer when it is combined with other cancer-causing agents, such as radon gas exposure plus smoking tobacco. Unlike chemical or physical triggers for cancer, ionizing radiation hits molecules within cells randomly. If it happens to strike a chromosome, it can break the chromosome, result in an abnormal number of chromosomes, inactivate one or more genes in the part of the chromosome that it hit, delete parts of the DNA sequence, cause chromosome translocations, or cause other types of chromosome abnormalities.

Damage normally results in the cell dying, but smaller damage may leave a stable, partly functional cell that may be capable of proliferating and developing into cancer, especially if tumor suppressor genes were damaged by the radiation.

Three independent stages appear to be involved in the creation of cancer with ionizing radiation: morphological changes to the cell, acquiring cellular immortality (losing normal, life-limiting cell regulatory processes), and adaptations that favor formation of a tumor. Even if the radiation particle does not strike the DNA directly, it triggers responses from cells that indirectly increase the likelihood of mutations. Medical use of ionizing radiation is a growing source of radiation-induced cancers. Ionizing radiation may be used to treat other cancers, but this may, in some cases, induce a second form of cancer. It is also used in some kinds of medical imaging. One report estimates that approximately 29,000 future cancers could be related to the approximately 70 million CT scans performed in the US in 2007. It is estimated that 0.4% of cancers in 2007 in the United States are due to CTs performed in the past and that this may increase to as high as 1.5–2% with rates of CT usage during this same time period. Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies[35]. Clear evidence establishes ultraviolet radiation, especially the non-ionizing medium wave UVB, as the cause of most non-melanoma skin cancers, which are the most common forms of cancer in the world. Non-ionizing radio frequency radiation from mobile phones, electric power transmission, and other similar sources have been described as a possible carcinogen by the World Health Organization's International Agency for Research on Cancer[36].

**Heredity:**

The vast majority of cancers are non-hereditary ("sporadic cancers"). Hereditary cancers are primarily caused by an inherited genetic defect. Less than 0.3% of the population are carriers of a genetic mutation which has a large effect on cancer risk and these cause less than 3–10% of all cancer[37]. Some of these syndromes include: certain inherited mutations in the genes BRCA1 and BRCA2 with a more than 75% risk of breast cancer and ovarian cancer,

and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) which is present in about 3% of people with colorectal cancer[38], among others.

**Physical agents**:

Some substances cause cancer primarily through their physical, rather than chemical, effects on cells[39]. A prominent example of this is prolonged exposure to asbestos, naturally occurring mineral fibers which are a major cause of mesothelioma, which is a cancer of the serous membrane, usually the serous membrane surrounding the lungs[40]. Other substances in this category, including both naturally occurring and synthetic asbestos-like fibers such as wollastonite, attapulgite, glass wool, and rock wool, are believed to have similar effects. Non-fibrous particulate materials that cause cancer include powdered metallic cobalt and nickel, and crystalline silica (quartz, cristobalite, and tridymite). Usually, physical carcinogens must get inside the body (such as through inhaling tiny pieces) and require years of exposure to develop cancer.

Physical trauma resulting in cancer is relatively rare. Claims that breaking bones resulted in bone cancer, for example, have never been proven. Similarly, physical trauma is not accepted as a cause for cervical cancer, breast cancer, or brain cancer[41].

One accepted source is frequent, long-term application of hot objects to the body. It is possible that repeated burns on the same part of the body, such as those produced by charcoal hand warmers, may produce skin cancer, especially if carcinogenic chemicals are also present. Frequently drinking scalding hot tea may produce esophageal cancer. Generally, it is believed that the cancer arises, or a pre-existing cancer is encouraged, during the process of repairing the trauma, rather than the cancer being caused directly by the trauma. However, repeated injuries to the same tissues might promote excessive cell proliferation, which could then

increase the odds of a cancerous mutation. There is no evidence that inflammation itself causes cancer.

**Hormones:**

Some hormones play a role in the development of cancer by promoting cell proliferation[42]. Insulin-like growth factors and their binding proteins play a key role in cancer cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis[43].

Hormones are important agents in sex-related cancers such as cancer of the breast, endometrium, prostate, ovary, and testis, and also of thyroid cancer and bone cancer. For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women without breast cancer. These higher hormone levels may explain why these women have higher risk of breast cancer, even in the absence of a breast-cancer gene. Similarly, men of African ancestry have significantly higher levels of testosterone than men of European ancestry, and have a correspondingly much higher level of prostate cancer. Men of Asian ancestry, with the lowest levels of testosterone-activating androstanediol glucuronide, have the lowest levels of prostate cancer. obese people have higher levels of some hormones associated with cancer and a higher rate of those cancers. Women who take hormone replacement therapyhave a higher risk of developing cancers associated with those hormones. On the other hand, people who exercise far more than average have lower levels of these hormones, and lower risk of cancer. Osteosarcoma may be promoted by growth hormones. Some treatments and prevention approaches leverage this cause by artificially reducing hormone levels, and thus discouraging hormone-sensitive cancers.

**Other Causes:**

Excepting the rare transmissions that occur with pregnancies and only a marginal few organ donors, cancer is generally not a transmissible disease. The main reason for this is tissue graft rejection caused by MHC incompatibility[44]. In humans and other vertebrates, the immune system uses MHC antigens to differentiate between "self" and "non-self" cells because these antigens are different from person to person. When non-self antigens are encountered, the immune system reacts against the appropriate cell. Such reactions may protect against tumour cell engraftment by eliminating implanted cells.

In the United States, approximately 3,500 pregnant women have a malignancy annually, and transplacental transmission of acute lymphoma, melanoma and carcinoma from mother to fetus has been observed. The development of donor-derived tumors from organ transplants is exceedingly rare. The main cause of organ transplant associated tumors seems to be malignant melanoma, that was undetected at the time of organ harvest.

**PATHOPHYSIOLOGY:**

Cancers are caused by series of mutations. Cancer is fundamentally a disease of regulation of tissue growth. In order for a normal cell to transform cell into a cancer cell growth and differentiation must be altered[45] .Genetic changes can occur at many levels, of entire chromosomes to a mutation affecting a single DNA nucleotide. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in many genes are required to transform a normal cell into a cancer cell[46]. There are two broad categories of genes which are affected by these change:

**Oncogenes:**

An oncogene is a gene that, when mutated or expressed at high levels, helps turn a normal cell into a tumor cell. Many abnormal cells normally undergo a programmed form of death (apoptosis). Activated oncogenes can cause those cells to survive and proliferate instead. Most oncogenes require an additional step, such as mutations in another gene, or environmental factors, such as viral infection, to cause cancer. Oncogens promotes cell growth through a variety of ways. Many can produce harmones, a "chemical messenger" between cell which encourage mitosis, the effects of which depends on the signal transduction of the receiving tissues or cells. In other words, when a hormone receptor on a recipient cell is stimulated, the signal is conducted from the cell to the cell nucleus to effect some change in gene transcription regulation at nuclear level. Mutations in proto-oncongens, which are normal gene that can become an oncogene due to mutations or increased expression. Proto-oncogenes code for proteins that help to regulate cell growth and differentiation. They can become an oncogene by a relatively small modification of its original function. After this the proto-oncogens become oncogens, and this transition upsets the normal balance of cell cycle regulation in the cell, making uncontrolled growth possible. One of the first oncogen to be defined in cancer research is the ras oncogens. mutation of this family of proto oncogene are more common being found in 20% to 30% of all human tumors.

**Tumor suppressor genes:**

These genes normally inhibit cell division and prevent survival of cells that have damaged DNA. In patients with cancer these tumor suppressor genes are often disabled. This is caused by cancer-promoting genetic changes. Typically, changes in many genes are required to transform a normal cell into a cancer cell. often DNA damage will cause the presence of free floating genetic material as well as other signs, and will trigger enzymes and pathways which lead to the activation

of tumor suppressor genes. the function of such gene is to arrest the progression of the cell cycle in order carry out DNA repair, preventing mutations from being passed on to the daughter cells. However the mutation can damage the tumor suppressor genes itself, or the signal pathway which activates it, "switching it off". Thus the DNA repair is hindered or inhibited: DNA damages accumulate without repair leading to cancer.

**SYMPTOMS OF CANCER:**

Cancer symptoms are quite varied and depend on where the cancer is located, where it has spread, and how big the tumor is. Some cancers can be felt or seen through the skin - a lump on the breast or testicle can be an indicator of cancer in those locations. Skin cancer (melanoma) is often noted by a change in a wart or mole on the skin. Some oral cancers present white patches inside the mouth or white spots on the tongue. Other cancers have symptoms that are less physically apparent. Some brain tumors tend to present symptoms early in the disease as they affect important cognitive functions. Pancreas cancers are usually too small to cause symptoms until they cause pain by pushing against nearby nerves or interfere with liver function to cause a yellowing of the skin and eyes called jaundice. Symptoms also can be created as a tumor grows and pushes against organs and blood vessels. For example, colon cancers lead to symptoms such as constipation, diarrhea, and changes in stool size. Bladder or prostate cancers cause changes in bladder function such as more frequent or infrequent urination. As cancer cells use the body's energy and interfere with normal hormone function, it is possible to present symptoms such as fever, fatigue, excessive sweating, anemia, and unexplained weight loss. When cancer spreads, or metastasizes, additional symptoms can present themselves in the newly affected area. Swollen or enlarged lymph nodes are common and likely to be present early. If cancer spreads to the brain, patients may experience vertigo, headaches, or seizures. Spreading to the

lungs may cause coughing and shortness of breath.

In addition, the liver may become enlarged and cause jaundice and bones can become painful, brittle, and break easily. Symptoms of metastasis ultimately depend on the location to which the cancer has spread.

**Symptom control:**

Although the control of the symptoms of cancer is not typically thought of as a treatment directed at the cancer, it is an important determinant of quality of life of cancer patients, and plays an important role in the decision whether the patient is able to undergo other treatments. Pain medications such as morphine and oxycodone and antiemetics, drugs to suppress nausea and vomiting are very commonly used in patients.

**DIAGNOSIS:**

Most cancers are initially recognized by signs or symptoms appear or through screening. Neither of these lead to definitive diagnosis. There are several methods of diagnosing cancer. With advances in technologies that understand cancers better, there is a rise of number of diagnostic tools that can help detect cancers. Once suspected, diagnosis is usually made by pathologists and oncopathologists and imaging radiologists. Some types of cancer, particularly lymphomas, can be hard to classify, even for an expert.

The most common diagnostic methods include:

- Biopsy

This is a test where a small sample of tissue is taken from the suspected cancer with the help of a fine tipped needle (fine needle aspiration – FNA), or with a thicker hollow needle (core biopsy) or by surgical excision. The tissues are then examined under a microscope for the presence of cancer cells. Depending on tumor

location, some biopsies can be done on an outpatient basis with only local anesthesia.

- Sentinel node biopsy

This is a procedure where the closest and most important nodes near the cancer are surgically excised and examined. Since sentinel nodes are the first location that cancer is likely to spread, only these lymph nodes that likely contain cancer cells.

- Endoscopy

In this imaging technique a thin, flexible tube with a tiny camera on the end is inserted into the body cavities. This allows the doctors to view the suspicious area. There are many types of scopes, each designed to view particular areas of the body

- Blood tests

Blood tests can be performed to detect the normal blood cells as well as for specific tumor markers. Some tumors release substances called tumor markers, which can be detected in the blood. A blood test for prostate cancer determines the amount of prostate specific antigen (PSA). Higher than normal PSA levels can indicate cancer

- Bone marrow aspiration

These show a picture of the bone marrow that may be affected in leukemia and blood cancers.

- Pap test

Pap test (Pap smear) is a routine test where a sample of cells from a woman's cervix is examined under the microscope. This helps identify changes in

the cells that could indicate cervical cancer or other conditions. Sputum analysis and bronchial washing analysis. The cells of the sputum and bronchial secretions are analyzed under the microscope for signs of lung and other respiratory cancers.

- Imaging studies

There are several imaging techniques. These include X rays, CT scans, MRI scans of various parts of the body. X-rays are the most common imaging techniques and they may be made more specific. This is used for detection of stomach and small intestinal growths and cancers. Mammogram is an X-ray of the breasts used to screen for and/or detect breast lumps and growths. A Magnetic Resonance Imaging (MRI) uses a powerful magnetic field to create detailed computer images of the body's soft tissue, large blood vessels and major organs. Both CT scan and MRI can also be used with contrast radio-labeled dyes to obtain a more clear and specific picture of the cancer. An Ultrasound uses high-frequency sound waves to determine if a suspicious lump is solid or fluid. These sound waves are transmitted into the body and converted into a computerized image. Bone scan is specifically used to identify and locate new areas of cancer spread to the bone. Normally a Positron imaging test (PET scan) is used.

- Genetic analysis

Cytogenetic analysis involves analysis of blood or bone marrow cells for organizations of chromosomes. This shows up any genetic mutations.

## Screening:

Unlike diagnosis efforts prompted by symptoms and medical signs, cancer screening involves efforts to detect cancer after it has formed, but before any noticeable symptoms appear. This may involve physical examination blood or urine tests, or medical imaging. Cancer screening is currently not possible for many types of cancers, and even when tests are available, they may not be recommended for everyone. Universal screening or mass screening involves

screening everyone. Selective screening identifies people who are known to be at higher risk of developing cancer, such as people with a family history of cancer. Several factors are considered to determine whether the benefits of screening outweigh the risks and the costs of screening.

These factors include:

- Possible harms from the screening test: for example, X-ray images involve exposure to potentially harmful ionizing radiation.
- The likelihood of the test correctly identifying cancer.
- The likelihood of cancer being present: Screening is not normally useful for rare cancers.
- Possible harms from follow-up procedures.
- Whether suitable treatment is available.
- Whether early detection improves treatment outcomes.
- Whether the cancer will ever need treatment.
- Whether the test is acceptable to the people: If a screening test is too burdensomethen people will refuse to participate.
- Cost of the test.

**TREATMENT:**

The most common types of cancer treatment, such

- **Surgery**

Surgery can be used to diagnose, treat, or even help prevent cancer in some cases. Most people with cancer will have some type of surgery. It often offers the greatest chance for cure, especially if the cancer has not spread to other parts of the body. Cancers can be cured if entirely removed by surgery removed by surgery but this is not always possible. When the cancer metastasized to other sites in the body prior to surgery, complete surgical excision is usually impossible. The goal of surgery is to remove the tumor alone or the entire organ.

- **Chemotherapy**

Chemotherapy (chemo) is the use of medicines or drugs to treat cancer. It s the treatment of cancer with cancer with drugs that can destroy cancer cells. It mainly refers to cytotoxic drugs affects rapidly dividing cells. Chemotherapy drugs with cell division in various ways, with duplication of DNA or the separation of the newly formed chromosomes. Most chemotherapy regimens are given in combination therapy. The treatment of some leukemia and lymphomas requires the use of high dose chemotherapy and total body irradiation.

**Principles of chemotherapy:**

Cancer is the controlled growth of calls coupled with malignant behavior, invasion and metastasis. Cancer is thought to be caused by the interaction between genetic susceptibilty and environmental toxins. Broadly, most of the chemotherapeutic drugs, work by impairing mitosis, effectively targeting fast-fasting deviding cells. As these drugs cause damage to cells they are termed as cytotoxic. Some of the drugs cause cells to undergo apoptosis. As chemotherapy effects after cell division, tumors with high growth fraction (such as acute myelogenous leukemia and aggressive lymphomas, including hodgkin's disease) are more sensitive to chemotherapy, as a larger proportion of the targeted cells are undergoing cell division at any time.

Recently, scientists have identified small pumps on the surface of cancer cells that actively more chemotherapy from inside the cell to the outside. Research on p-glycoproteins and other such chemotherapy efflux pumps, is currently ongoing. Medications to inhibit the function of p-glycoprotein are undergoing testing as of june 2007, to enhance the efficacy of chemotherapy.

## Treatment schemes:

There are a number of strategies in the administration of chemotherapeutic drugs used today. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms.

Combined modality chemotherapy is the use of drugs with other cancer treatments , such as radiation therapy or surgery. Combination therapy is a similar practice which involves treating a patients with a number of different drugs simultaneously. The drugs differ in their mechanism and side effects. The biggest advantage is the minimizing the chances of resistances developing to any one agent.

Adjuvant chemotherapy can be used when there is little evidence of cancer present, but there is risk of recurrence. This can help reduce chances of resistance developing if the tumor does develop. It is also useful in killing any cancerous cells which have spend to other parts of the body. This is often effective as the newly growing tumours are fast dividing and therefore very susceptible. In neoadjuvant chemotherapy initial chemotherapy is aimed for striking the primary tumor, therby rendering local therapy less destructive or more effective.

Palliative chemotherapy is given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, a better toxicity profile is generally expected. For some cancers, chemotherapy can completely get rid of the cancer with a good chance that it will never come back. Examples include certain types of lymphoma, leukemia and testicular cancer, among others. For most cancers that have metastasized (spread beyond the original cancer site), chemotherapy cannot cure the cancer. However, chemotherapy may be helpful in shrinking the cancer, improving or completely eliminating distressing symptoms caused by the cancer for a period of time and helping you live longer.

The majority of chemotherapeutic drugs can be divided into:

- Alkylating agents,

- Antimetabolities,
- Anthracyclines,
- Plant alkaloids,

Topoisomer inhibitors and other antitumour agents all of these drugs affect cell division synthesis and function in some way. Some newer agents do not interfere with DNA. These include monoclonal antibodies and new tyrosine inase inhibitors. In, addition some drugs which modulate tumor cell behavior without directly attacking those cells. Harmone treatments fall into this category of adjuvant therapies.

**Alkylating agents:**

These agents are so named because of their ability to add alkyl groups to many electronegative grouos under conditions present in cells. Cisplatin and carbplatin, as well as oxaliplatin are alkylating agents.Other agents are mechloethamine, cyclophosphamide, chlorambucil. They work by chemically modifying a cell's DNA.

**Anti-metabolites:**

Anti-metabolites masquerade as purine or pyrimide – which become the building blocks of DNA. They prevent these substances becoming incorporated into DNA during the "s" phase, stopping normal development and division. They also affect RNA synthesis. Due to thei efficiency, these drugs are the most widely used cytostatics.

**Antitumor antibiotics:**

The most important immunosuppressant from this group is dactinomycin, which is used in kidney transplatations.

- **Radiation Therapy**

Radiation therapy uses high-energy particles or waves to destroy or damage cancer cells. It is one of the most common treatments for cancer, either by itself or along with other forms of treatment. Radiation therapy also called as radiotherapy or irradiation, is the use of ionizing radiation to kill cancer cells and shrink tumors. Radiation therapy can be administered externally via external beam radiotherapy or internally via branchy therapy. The effects of radiation therapy are localized and confined to the region being treated.

Radiation therapy injures or destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to grow and divide. Radiation therapy may be used to treat almost every type of solid tumor, including cancers of the brain, breast, cervix, larynx, lung, pancreas, prostrate, skin, stomach, uterus, or soft tissues sarcomas.

- **Targeted Therapy**

Targeted therapy is a newer type of cancer treatment that uses drugs or other substances to more precisely identify and attack cancer cells, usually while doing little damage to normal cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, over expressed, or otherwise critical proteins within the cancer cell. Eg.tyrosine kinase inhibotrs inmatinib and gefitinib. Monoclonal antibody therapy is another in which the therapeutic agent is an antibody which specially binds to a proteinon the surface of cancer cells.

- **Immunotherapy:**

It refers to a diverse set of therapeutic stratagies designed to induce the patient's own immune system to fight the tumor. Allogenic hematopoietic stem cell transplantation can be considered a form of immunotherapy, since the donor's immune cells will often attack the tumor in phenomenon known as graft-versus-

tumor.

- **Harmonal Therapy:**

The growth of some cancers can be inhibited by providing or blocking certain harmones. Common examples of harmone-sensitive tumors includes certain types of breast and prostrate cancer. Removing or blocking estrogens or testosterones is often an important additional treatment. In certain cancers, administration of harmone agonist.

**ETIOLOGY:**

- **Chemical carcinogens:**

Chemical carcinogens that cause DNA mutations are known as mutagens and mutagens that causes cancers known as carcinogens. Tobacco smoking is associated with lung cancer and bladder cancer. Prolonged exposure to asbestos fibers is associated with mesothelioma.

- **Ionizing radiation:**

Sources of ionizing radiation, such as radon gas, can cause cancer. Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies.

- **Hormonal imbalances:**

Some hormones can act in a similar manner to non-mutagenic carcinogens in that they may stimulates excessive cell growth. Examples is the role of hyperestrogenic stages in promoting endometrial cancer.

- **Immune system dysfunction:**

HIV is associated with a number of malignancies, including non-Hodgkin's lymphoma, HPV- associated malignancies such as anal cancer and cervical cancer

- **Infectious diseases:**

The main viruses associated with human cancers are human papillomavirus, hepatitis C and hepatitis B virus, Epstein-Barr virus, and human T-lymphotropic

virus. Experimental and epidemiological data imply a causative role for viruses and they appear to be the second most important risk factors for cancer development in humans, exceeded only by tobacco usage. Liver cirrhosis, from chronic viral hepatitis infection or alcoholism, is associated with the development of liver cancer.

In addition to viruses, researchers have noted a connection between bacteria and certain cancers. The prominent eg. is chronic infection wall of the stomach with helicobacter pylori and gastric cancer.

- **Alternative treatments:**

Complementary and alternative cancer treatments are a diverse group of health care systems, practices, and products that are not part of conventional medicine[51]."Complementary medicine" refers to methods and substances used along with conventional medicine, while "alternative medicine" refers to compounds used instead of conventional medicine[52].Most complementary and alternative medicines for cancer have not been rigorously studied or tested. Some alternative treatments have been investigated and shown to be ineffective but still continue to be marketed and promoted[53].

## Prevention of cancer:

Cancer prevention is defined as active measures to decrease the risk of cancer. The vast majority of cancer cases are due to environmental risk factors, and many, but not all, of these environmental factors are controllable lifestyle choices. Thus, cancer is considered a largely preventable disease. Greater than 30% of cancer deaths could be prevented by avoiding risk factors including: tobacco, overweight / obesity, an insufficient diet, physical inactivity, alcohol, sexually transmitted infections, and air pollution.

Not all environmental causes are controllable, such as naturally occurring background radiation, and other cases of cancer are caused through hereditary

genetic disorders, and thus it is not possible to prevent all cases of cancer.

- **Dietary**

While many dietary recommendations have been proposed to reduce the risk of cancer, the evidence to support them is not definitive. The primary dietary factors that increase risk are obesity and alcohol consumption; with a diet low in fruits and vegetables and high in red meat being implicated but not confirmed. Consumption of coffee is associated with a reduced risk of liver cancer. Consumption of red or processed meat may lead to an increased risk of breast cancer, colon cancer, and pancreatic cancer, a phenomenon which could be due to the presence of carcinogens in meats cooked at high temperatures.

Dietary recommendations for cancer prevention typically include an emphasis on vegetables, fruit, whole grains, and fish, and an avoidance of processed and red meat (beef, pork, lamb), animal fats, and refined carbohydrates.

- **Medication**

The concept that medications can be used to prevent cancer is attractive, and evidence supports their use in a few defined circumstances. In the general population NSAIDs reduce the risk of colorectal cancer however due to the cardiovascular and gastrointestinal side effects they cause overall harm when used for prevention. Aspirin has been found to reduce the risk of death from cancer by about 7%.COX-2 inhibitor may decrease the rate of polyp formation in people with familial adenomatous polyposis however are associated with the same adverse effects as NSAIDs. Daily use of tamoxifen or raloxifene has been demonstrated to reduce the risk of developing breast cancer in high-risk women. The benefit verses harm for 5-alpha-reductase inhibitor such as finasteride is not clear. Vitamins have not been found to be effective at preventing cancer, although low blood levels of vitamin D are correlated with increased cancer risk. Whether this relationship is causal and vitamin D supplementation is protective is not determined. Beta-

Carotene supplementation has been found to increase lung cancer rates in those who are high risk. Folic acid supplementation has not been found effective in preventing colon cancer and may increase colon polyps.

- **Vaccination**

Vaccines have been developed that prevent some infection by some viruses.Human papillomavirus vaccine (Gardasil and Cervarix) decreases the risk of developing cervical cancer. The hepatitis B vaccine prevents infection with hepatitis B virus and thus decreases the risk of liver cancer.

**CANCER PAIN:**

People with cancer often feel severe or constant pain. The pain they experience depends on the type of cancer they have, the stage the disease is at, and the therapy they receive. Approximately 25% to 50% of people with cancer complain of pain at the time of diagnosis, and up to 75% of people with cancer complain of pain as the cancer progresses. Cancer pain can be defined as a complex sensation that reflects both damage to the body and the body's response to the damage. Pain is one of the major complications of cancer. At any given time, about half of all patients with malignant cancer are experiencing pain, and more than a third of those experience moderate or severe pain that diminishes their quality of life by adversely affecting mood, sleep, social relations and activities of daily living[54]. The presence of pain depends on the location of the cancer and the stage of the disease. Two thirds of patients with advanced stage cancer experience significant pain[55].

## Causes of Cancer Pains:

Most cancer pain is caused by the tumour pressing on bones, nerves or other organs in your body. Sometimes pain is related to your cancer treatment. For example, some chemotherapy drugs can cause numbness and tingling in your hands and feet or a burning sensation at the place where they are injected.

Radiotherapy can cause skin redness and irritation. Between 40 and 80 percent of patients with cancer pain experience neuropathic pain[56].

Cancer pain can be caused by:

✓ **INFECTION:**

Infection of a tumor or its surrounding tissue can cause rapidly escalating pain, but is sometimes overlooked as a possible cause of pain.

✓ **TUMOR-RELATED:**

Tumors can cause pain by crushing or infiltrating tissue, or by releasing chemicals that make nociceptors responsive to stimuli that are normally non-painful.

✓ **VASCULAR EVENTS:**

- Deep vein thrombosis

Between 15 and 25 percent of deep vein thrombosis (DVT) is caused by cancer (often by a tumor compressing a vein). Cancers most likely to cause DVT are pancreatic cancer, stomach cancer, brain tumors, advanced breast cancer and advanced pelvic tumors. DVT may be the first hint that cancer is present. It causes swelling and pain in the legs, especially the calf, and (rarely) in the arms.[57]

- Superior vena cava syndrome

The superior vena cava may be compressed by a tumor, most often non-small-cell lung carcinoma small-cell lung carcinoma , lymphoma, or metastasis, causing superior vena cava syndrome. Common symptoms include shortness of breath, swelling of the face and neck, dilation of veins in the neck and chest, and chest wall pain[58].

✓ **NERVOUS SYSTEM:**

- Brain

Brain tissue itself contains no nociceptors; brain tumors cause pain by pressing on blood vessels or the membrane that encapsulates the brain, or indirectly by causing a build-up of fluid which may compress pain-sensitive tissue.

- Meninges

Ten percent of patients with disseminated cancer develop meningeal carcinomatosis, where metastatic seedlings develop in the meninges (outer lining) of both the brain and spinal cord (with possible invasion of the brain or spinal

cord). Melanoma and breast and lung cancer account for 90 percent of such cases. Back pain and headache – often severe and possibly associated with nausea, vomiting, neck rigidity and pain or discomfort in the eyes due to light exposure (photophobia) – are frequently the first symptoms of meningeal carcinomatosis. "Pins and needles" (paresthesia), bowel or bladder dysfunction and lower motor neuron weakness are common features.[59]

- Spinal cord compression

About three percent of cancer patients experience spinal cord compression, usually from expansion of the vertebral body due to metastasis, sometimes involving collapse of the vertebral body. Occasionally compression is caused by nonvertebral metastasis adjacent to the spinal cord. Seventy percent of cases involve the thoracic, 20 percent the lumbar, and 10 percent the cervical spine; and about 20 percent of cases involve multiple sites of compression. The nature of the pain depends on the location of the compression.[60]

- Nerve infiltration or compression

Infiltration or compression of a nerve by a primary tumor causes peripheral neuropathy in one to five percent of cancer patients.

- Dorsal root ganglion inflammation

Small-cell lung cancer and, less often, cancer of the breast, colon or ovary may produce inflammation of the dorsal root ganglia precipitating burning, tingling pain in the extremities, with occasional "lightning" or lancinating pains.[61]

- Brachial plexopathy

Brachial plexopathy is a common product of Pancoast tumor, lymphoma and breast cancer, and can produce severe burning dysesthesic pain on the back of the hand, and cramping, crushing forearm pain.

✓ **BONE:**

Invasion of bone by cancer is the most common source of cancer pain. About 70 percent of breast and prostate cancer patients, and 40 percent of those with lung, kidney and thyroid cancers develop bone metastases. It is commonly felt as tenderness, with constant background pain and instances of spontaneous or

movement-related exacerbation, and is frequently described as severe.

Tumors in the marrow instigate a vigorous immune response which enhances pain sensitivity, and they release chemicals that stimulate nociceptors. As they grow, tumors compress, consume, infiltrate or cut off blood supply to body tissues, which can cause pain.[62]

- Fracture

Rib fractures, common in breast, prostate and other cancers with rib metastases, can cause brief severe pain on twisting the trunk, coughing, laughing, breathing deeply or moving between sitting and lying. In breast, prostate or lung cancer, multiple myeloma and some other cancers, sudden onset limb or back pain may indicate pathological bone fracture .[63]

- Skull

The base of the skull may be affected by metastases from cancer of the bronchus, breast or prostate, or cancer may spread directly to this area from the nasopharynx and this may cause headache, facial paresthesia, dysesthesia or pain, or cranial nerve dysfunction – the exact symptoms depending on the cranial nerves impacted.

- Pelvis

Pain produced by cancer within the pelvis varies depending on the affected tissue, but it frequently radiates diffusely to the upper thigh, and may refer to the lumbar region. Lumbosacral plexopathy is often caused by recurrence of cancer in the presacral space, and may refer to the external genitalia or perineum. Local recurrence of cancer attached to the side of the pelvic wall may cause pain in one of the iliac fossae. Pain on walking that confines the patient to bed indicates possible cancer adherence to or invasion of the iliacus muscle.

Pain in the hypogastrium (between the navel and pubic bone) is often found in cancers of the uterus and bladder, and sometimes in colorectal cancer especially if infiltrating or attached to either uterus or bladder.

- Viscera

Visceral pain is diffuse and difficult to locate, and is often referred to more distant, usually superficial, sites.

- Liver

Acute hemorrhage into a hepatocellular carcinoma causes severe upper right quadrant pain, and may be life-threatening, requiring emergency surgery or other emergency intervention. A tumor can expand the size of the liver several times and consequent stretching of its capsule can cause aching pain in the right hypochondrium.

Other causes of pain in enlarged liver are traction of the supporting ligaments when standing or walking, the liver pressing against the rib cage or pinching the wall of the abdomen, and straining the lumbar spine. In some postures the liver may pinch the parietal peritoneum against the lower rib cage, producing sharp, transitory pain, relieved by changing position. The tumor may also infiltrate the liver's capsule, causing dull, and sometimes stabbing pain.

- Kidneys and spleen

Cancer of the kidneys and spleen produces less pain than that caused by liver tumor – kidney tumors eliciting pain only once the organ has been almost totally destroyed and the cancer has invaded the surrounding tissue or adjacent pelvis. Pressure on the kidney or ureter from a tumor outside the kidney can cause extreme flank pain.

Local recurrence of cancer after the removal of a kidney can cause pain in the lumbar back, or L1 or L2 spinal nerve pain in the groin or upper thigh, accompanied by weakness and numbness of the iliopsoas muscle, exacerbated by activity.

✓ **ABDOMINAL AND UROGENITAL HOLLOW ORGANS**

Inflammation of artery walls and tissue adjacent to nerves is common in tumors of abdominal and urogenital hollow organs. Infection or cancer may irritate the trigone of the urinary bladder, causing spasm of the detrusor urinae muscle (the muscle that squeezes urine from the urinary bladder), resulting in deep pain above

the pubic bone, possibly referred to the tip of the penis, lasting from a few minutes to half an hour.

- Gastrointestinal

The pain of intestinal tumors may be the result of disturbed motility, dilation, altered blood flow or ulceration. Malignant lymphomas of the gastrointestinal tract can produce large tumors with significant ulceration and bleeding.

- Pancreas

Ten percent of patients with cancer of the pancreatic body or tail experience pain, whereas 90 percent of those with cancer of the pancreatic head will, especially if the tumor is near the hepatopancreatic ampulla. The pain appears on the left or right upper abdomen, is constant, and increases in intensity over time. It is in some cases relieved by leaning forward and heightened by lying on the stomach. Back pain may be present and, if intense, may spread left and right. Back pain may be referred from the pancreas, or may indicate the cancer has penetrated paraspinal muscle, or entered the retroperitoneum and paraaortic lymph nodes

- Rectum

A local tumor in the rectum or recurrence involving the presacral plexus may cause pain normally associated with an urgent need to defecate. This pain may, rarely, return as phantom pain after surgical removal of the rectum, though pain within a few weeks of surgical removal of the rectum is usually neuropathic pain due to the surgery . The emergence of pain on standing or walking (described as "dragging") may indicate a deeper recurrence involving attachment to muscle or fascia.

- Serous mucosa

Carcinosis of the peritoneum may cause pain through inflammation, disordered visceral motility, or pressure of the metastases on nerves. Once a tumor has penetrated or perforated hollow viscera, acute inflammation of the peritoneum appears, inducing severe abdominal pain. Pleural carcinomatosis is normally painless.

- Soft tissue

Invasion of soft tissue by a tumor can cause pain by inflammatory or mechanical stimulation of nociceptors, or destruction of mobile structures such as ligaments, tendons and skeletal muscles.

**ACUTE AND CHRONIC PAIN:**

Cancer pain can be acute or chronic. Acute pain is due to damage caused by an injury and tends to only last a short time. For example, having an operation can cause acute pain. The pain goes when the wound heals. In the meantime, painkillers will usually keep it under control. Chronic pain is pain caused by changes to nerves. Nerve changes may occur due to cancer pressing on nerves or due to chemicals produced by a tumour. It can also be caused by nerve changes due to cancer treatment. The pain continues long after the injury or treatment is over and can range from mild to severe. It can be there all the time and is also called persistent pain. Chronic pain can be difficult to treat, but painkillers or other pain control methods can successfully control it in about 95 out of every 100 people (95%).

Pain that is not well controlled can develop into chronic pain. So it is important to take painkillers that you are prescribed. If there is chronic cancer pain, and when the pain is not controlled by the medicines that are taken. This is called breakthrough pain. If regularly painkillers are taken but still get pain at times extra top up doses of painkillers may be needed. Sometimes pain can come on quickly, for example when you need to have a dressing changed or move around. This type of pain is called incident pain.

**Physical cancer pain:**

Physical cancer pain has two sources:

- Nociceptive pain refers to pain relayed by nerves with the job of conveying damage in a part of the body. The pain is usually felt as aching or pressure -

most cancer pain feels like this.

- Neuropathic (nerve) pain refers to pain caused by damage inside the nervous system. The pain is usually felt as sharp shooting and stabbing sensations

**TYPES OF CANCER PAIN:**

Pain can be described in different ways. They may be acute and chronic pain. Or they may be the body tissue your pain comes from. It is extremely important to find out the type and cause of pain so that they can be treated in the right way.

Types of pain include:

- Nerve pain
- Bone pain
- Soft tissue pain
- Phantom pain
- Referred pain
- **Nerve pain**

Nerve pain is caused by pressure on nerves or the spinal cord, or by damage to nerves. It is also called neuropathic pain. People often describe nerve pain as burning, shooting, tingling, or as a feeling of something crawling under their skin. It can be difficult to describe exactly how it feels. Some people have long term nerve pain after surgery. Nerves are cut during surgery and they take a long time to heal because they grow very slowly. Some people may have pain around their scar for 2 years or more after their surgery. Nerve pain can also occur after other cancer treatments such as radiotherapy or chemotherapy.

- **Bone pain**

Cancer can spread into the bone and cause pain. The cancer may affect one specific area of bone or several areas. The cancer cells within the bone damage the bone tissue and cause the pain. This pain is called somatic pain which can be described as aching, dull or throbbing.

- **Soft tissue pain**

Soft tissue pain means pain from a body organ or muscle. For eg, you may have pain in your back caused by tissue damage to the kidney. This pain can't always pinpoint, but it is usually described as sharp, cramping, aching, or throbbing. Soft tissue pain is also called visceral pain.

- **Phantom pain**

Phantom pain means pain in a part of the body that has been removed. For example, pain in an arm or leg that has been removed due to sarcoma or osteosarcoma. Or pain in the breast area after removal of the breast (mastectomy). Phantom pain is very real and people sometimes describe it as unbearable.

- **Referred pain**

Sometimes pain from an organ in the body may be felt in a different part of the body. This is called referred pain. For example, a swollen liver may cause pain in the right shoulder, even though the liver is under the ribs on the right side of the body. This is because the liver presses on nerves that end in the shoulder.

Cancer pain affects quality of life in four main ways:

- physically (people feel weak)
- psychologically (people feel unable to cope)
- socially (people's relationships suffer)
- spiritually (suffering may make people question their beliefs)

**TREATMENT FOR CANCER PAIN:**

**PAIN KILLERS USED:**

- **Opioids:**

Opioids are most commonly used for pain relief and while some of the adverse effects seen with initial therapy are short term, some may last for longer durations, especially when therapy is continued over longer periods. Some of the opiods used for severe pain are morphine, diamorphine, fentanyl, alfentanil,

buprenorphine, oxycodone, hydromorphone, methadone and for moderate or mild pain codeine, tramadol[64].

Some of the adverse effects of opioid use include:

- Nausea and vomiting:

The use of opioids stimulates opioid receptors present in the gastrointestinal tract as well as in the vomiting centre of the brain to cause nausea and vomiting.

- Drowsiness or sedation:

Opioids, and in particular morphine, are known to cause severe sedation and drowsiness.

- Skin changes:

An allergic reaction called urticaria may develop and cause a skin rash characterized by red, itchy, raised bumps. This is caused by the release of histamine in response to opioid use.

- Constipation:

Opioids cause sluggish peristaltic movements in the digestive tract. This causes stasis or loss of movement of the intestinal contents and leads to severe constipation, especially in the case of long-term use.

- Respiratory depression:

The breathing mechanism in response to a low blood oxygen level may be suppressed. As blood oxygen falls and blood carbon dioxide rises, there is an increase in drive for respiration.

- Psychological effects:

Opioids give rise to a sense of euphoria and may also lead to hallucinations, delirium, dizziness and confusion. There may be some amount of memory loss and headache.

- Changes in heart rate:

Heart rate may become either rapid or very slow. Some opioid users may also develop postural hypotension or a severe fall in blood pressure on standing up from a sitting or lying position.

- Spasms:

Some people may develop spasms of the ureter and urinary retention or biliary colic and spasms of the biliary tree.

**Some of the opiods used** :

- For severe pain

  morphine, diamorphine, fentanyl, alfentanil, buprenorphine, oxycodone, hydromorphone, methadone are used.

- For moderate or mild pain

  codeine, tramadol are used.

➢ **Non opiods**

Non opiods analgesics are useful for acute or chronic pain resulting from a variety of diseases process such as cancer, arthritis, trauma, surgery. After the administration of Non-opiods there will not be a need of additional analgesia. they does not produce physical or psychological dependence and therefore sudden interruption in treatment does not cause drug withdrawals. Non-opioid analgesics are pain medications for mild to moderate pain.

Non-opioid analgesics include NSAIDs, such as ibuprofen, as well as other analgesics such as acetaminophen and aspirin. [65] These medications also include adjuvant analgesics, which are those that relieve pain even though pain relief is not their primary purpose. Examples include antidepressants and anticonvulsants, both regularly used to treat certain types of chronic pain.

Non-opioid analgesics may be short-acting or long-acting pain medications. They may be taken alone for pain management, though they may also be taken in

combination with opioids to relieve moderate to severe pain.

A part of analgesics binds to the opioid-receptors and form a separate group. Substances with analgesic, antipyretic and antiphlogistic effects

## Non-acidic analgesics

- Not anti-inflammatory in therapeutic doses
- Possess much lower plasma protein-binding capacities than acidic analgesics
- Are derivatives of phenazone, metamizole, paracetamol

Non-opioid analgesics also used to be referred to as less effective analgesics. This is not completely correct concerning their properties because particularly in inflammation-associated nociceptive pain their analgesic effect if often better than that of strong or moderately strong opioids.

**Mechanism of action of non-acidic analgesics:**

Rapid penetration through the blood-brain barrier with secondary inhibiton of nociceptive stimuli induce the release of prostaglandins at spinal cord and CNS level.

## Acid analgesics:

**Mechanisms of action of acidic analgesics:**

NSAIDs reduce prostaglandin synthesis by inhibition of cyclooxygenase (COX 1 and COX 2).

**COX 1**

- Activated by physiological stimuli
- Exerts its function in healthy tissues

**COX 2**

- Activated mainly by inflammation stimuli
- Releases inflammatory mediators
- Occurs physiologically in spinal cord, kidney and uterus

- Physiological action in adaptation processes (e.g. wound healing)

Inhibition of COX 2 is responsible for the analgesic, antipyretic and anti-inflammatory effects, side effects are mainly due to inhibition of COX 1.

## Side effects caused by the inhibition of cyclooxygenase:

Prostaglandin effects:

- ✓ Decreased secretion of gastric juice
- ✓ Cell protection
- ✓ Decreased bowel motility
- ✓ Increased platelet aggregation by thromboxane A2.

Effect of prostaglandin synthesis inhibitors:

- ✓ Increased secretion of gastric juice
- ✓ Increased bowel motility
- ✓ Decreased renal excretion of sodium ions, water retention
- ✓ Oedema
- ✓ Inhibition of platelet aggregation
- ✓ In case of COX inhibition, the effect of lipoxygenase is activated.

Clinical effects:

- ✓ In asthmatic patients, an asthmatic attack may be triggered
- ✓ Headaches
- ✓ Vertigo
- ✓ Gasric mucosa irritation
- ✓ Peptic ulceration
- ✓ oedema

## Possible side effects independent of cyclooxygenase inhibition

- Toxic damage to bone marrow (aplastic anaemia, thrombocytopenia)
- Allergic and anaphylactic reactions
- Hepatotoxic reactions
- Gastro-intestinal ulcers
- Asthma
- Bleeding disorders
- Last weeks of pregnancy → preterm closure of Botallo's duct.

- Severe hepatic or renal dysfunction → caution is advised if NSAIDs are administered

## Drug interactions[66]:

| | |
|---|---|
| Glucocorticoids | Risk of gastro-intestinal complications ↑ |
| Probenecid<br>(therapy of gout) | Excretion of uric acid ↑<br>Excretion of NSAIDs ↓ |
| Saluretics<br>(to promote uric acid excretion) | Diuretic effect ↓ |
| Oral antidiabetics | Blood sugar reducing effect ↑ |
| Methotrexate<br>(cytostatic) | Elimination ↓<br>Toxicity of methotrexate ↑ |
| Li+<br>(psychopharmacology) | Elimination ↓ |
| Cumarin derivatives | Anti-coagulation effect ↑<br>Risk of bleeding ↑ |
| ACE inhibitors | Antihypertensive effect ↑ |

Some of the non opiod analgesic drugs are

- ✓ Aspirin,
- ✓ ibuprofen,
- ✓ diclofenac,
- ✓ naproxen,
- ✓ flupiritin,
- ✓ Tylenol

# DRUG PROFILE:

## NAPROXEN:

**DECRIPTION:**

It is a non steroidal anti-inflammatory drug (NSAID). It works by reducing hormones that cause inflammation and pain in the body. Naproxen is used to treat pain or inflammation caused by conditions such as cancer, arthritis, alkylosing spondylitis, tendinitis, bursitis, gout, or menstrual cramps.

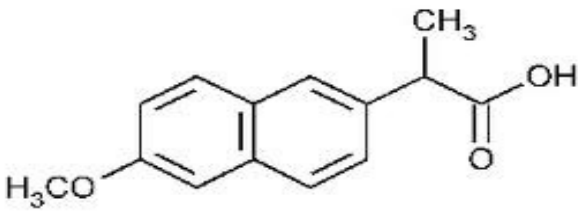
**Chemical name:** Naproxen is (+)-(S)-2-(6-methoxynaphthalen-2- yl) propanoic acid.

**Molecular formula :**C14H14O3.

**Molecular Weight:** Average: 230.2592

Monoisotopic: 230.094294314

**Structure:**




**Brand name:** Anaprox, Naprelan, Naprosyn, Aleve.

**CLINICAL PHARMACOLOGY:**[68]

- **Mechanism of action:**

Naproxen is a phenylpropionic acid derivatives having analgesic, anti inflammatory and anti pyretic activity. Such activity is thought to be mediated via inhibition of the enzyme complex prostagladin synthetase with consequent reduction in the synthesis of prostagladin from arachidonic acid. The onset of action of naproxen may be 2 or more hopurs after oral administration with therpeutics effect persisting for upto 7-8 hours .

- **Absorption:**

It is rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak concentration (Cmax); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even with the observed differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days and the degree of naproxen accumulation is consistent with this half-life

- **Distribution**

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels
due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough Cs 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma.

- **Metabolism**

It is extensively metabolized in the liver to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

- **Excretion**

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen ( < 1%), 6-0-desmethyl naproxen ( < 1%) or their conjugates (66% to 92%). The

plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. Small amounts, 3% or less of the administered dose, are excreted in the feces.

**INDICATIONS:**

It is indicated for the relief of symptoms associated with rheumatoid arthritis, osteoarthritis, juvenile arthritis acute and chronic gout and for cancer pain.

**CONTRAINDICATIONS:**

Active peptic ulceration and sensitivity to naproxen, aspirin, or other non-steroidal anti inflammatory agents.It is contraindicated in patients with gasterointestinal ulceration, haemorrahagic diathesis and asthma and in liver dydfunction.

**DOSAGE AND ADMINISTRATION:**

After observing the response to initial therapy with NAPROSYN, ECNAPROSYN, ANAPROX, ANAPROX or Suspension, the dose and frequency should be adjusted to suit an individual patient's needs. The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and adverse events. A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients.

**ROUTE OF ADMINISTRATION:**

Use readily available oral tablets, capsules, or liquid. During intervals of nausea and vomiting, use suppositories, unless the nausea is NSAID related. Ketorolac tromethamine is the only NSAID available for parenteral use.

**DRUG INTERACTIONS:**

ACE-inhibitors, Aspirin, Diuretics, Lithium, Methotrexate, Warfarin

**ADVERSE REACTIONS:**

**Body as a Whole**:

Pain (back), pain, infection, fever, injury (accident), asthenia, pain chest, headache , flu syndrome, monilia, neck rigid, pain neck, abdomen enlarged, carcinoma, cellulitis, membrane disorder, allergic reaction.

**Gastrointestinal:**

Nausea, diarrhea, constipation, abdominal pain, flatulence, gastritis, vomiting, dysphagia, dyspepsia (14%), heartburn. stomatitis.

**Hematologic:**

Anemia, ecchymosis.

**Respiratory:**

Pharyngitis, rhinitis, sinusitis, bronchitis, cough increased.

**Renal:**

Urinary tract infection, cystitis.

**Dermatologic:**

Skin rash, skin eruptions, ecchymoses, purpura.

**Metabolic and Nutrition:**

Peripheral edema, hyperglycemia.

**Central Nervous System:**

Dizziness, paresthesia, insomnia, drowsiness, light headedness.

**Cardiovascular:**

Hypertension, edema, dyspnea, palpitations.

**Musculoskeletal:**

Cramps(leg), myalgia, joint disorder, tendon disorder.

**Special Senses:**

Tinnitus, hearing disturbances, visual disturbances.

# Special Populations

- **Pediatric Patients**

In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see DOSAGE AND ADMINISTRATION) were found to be similar to those found in normal adults following a 500 mg dose

- **Geriatric Patients**

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects.

The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

# FLUPIRTINE

**DISCRIPTION:**

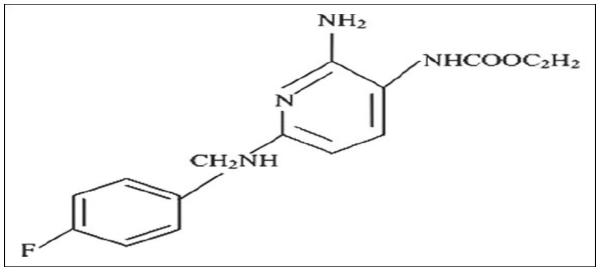
Flupirtine is an aminopyridine that functions as a centrally acting non-opioid analgesic. It is unique as a non-opioid, non-NSAID, non-steroidal analgesic.[67]

**chemical name:** ethyl-N-{2-amino-6-(4- fluorophenylmethylamino) pyridine-3 yl} cabamate

**molecular Formula:** $C_{15}H_{17}FN_4O_2$

**Molecular mass:** 304.32 g/mol

**Structure:**




**Brand names:** katodol, lupirtine.

**PHARMACOKINETICS :**[69]

- **Mechanism of action:**

Flupirtine is a selective neuronal potassium channel opener that also has NMD receptor antagonist properties

- **Absorption**

It is completely absorbed from gastrointestinal tract with a bioavailability of 90% by oral route and 70% by rectal route.

- **Distribution**

Flupirtine has large volume of distribution (Vd) and gets equally distributed into both extra and intravascular compartments. Flupirtine is 80–84% bound to human albumin. Concentration in CSF is same as that in plasma

and higher concentration was observed in liver and exocrine glands, whereas lower concentration was observed in the kidney. The half-life of flupirtine on oral, intravenous, and rectal administration with 100 mg is 6.5, 8.5, and 10.7.

- **Metabolism and elimination**

Flupirtine is metabolized in liver to 4-Fluorohippuric and N-acetylated analogue by peroxidase enzymes [human myeloperoxidase and horse radish peroxide (HRP)]. The N-acetylated metabolite retains 20–30% of activity of its parent compound. The two metabolites are further oxidized and then conjugated with glycine to form inactive metabolites 72% of the total dose administered appears in urine as parent drug and its metabolites, whereas 18% is excreted in feces.

**DOSAGE AND ADMINISTRATION:**

Flupirtine can be administered by oral and rectal routes. It is available as 50 and 100 mg for oral administration. Adult dose is 300–400 mg per day and can be increased to 600 mg per day. Dose in children is 150–200 mg per day in 3–4 divided doses.

**SPECIAL POPULATIONS:**

Safety of flupirtine in pregnant, lactating women, and children less than 6 years is not established. If indicated in lactating women, breastfeeding should be stopped. Dose of flupirtine should be reduced to 50% in elderly patients and those with renal and hepatic impairment.

**DRUG INTERACTION:**

Flupirtine has shown to increase warfarin toxicity but the mechanism is not clear; hence, patients on oral anticoagulant therapy should be monitored for prothrombin time and increases hepatotoxic potential of paracetamol hepatic transaminases levels should be monitored when both the drugs are given concomitantly. Alcohol and sedatives including benzodiazepines potentiate tiredness dizziness due to flupirtine.

**CONTRAINDICATION:**

Flupirtine is avoided in patients with history of hypersensitivity to flupirtine, hepatic encephalopathy, cholestasis, myasthenia gravis, chronic alcoholism, primary biliary cirrhosis, and liver disease

**ADVERSE DRUG REACTIONS:**[70]

Fluriptine is notably devoid of any addictive properties, negative psychological or motor function effects, or effects on reproductive function.

It can be broken up into two categories.

- **PERIPHERAL SIDE EFFECT**

Blurred visions, Constipation, Diarrhoea, Dry mouth, Flu-like symptoms, Gastric and abdominal discomfort, Gastric fullness, Heart burn, Nausea, Pruritus, Vomiting

- **CARDIOVASCULAR EFFECTS:**

Slight decreases in systolic blood pressure have been reported in patients receiving chronic flupirtine therapy. Isolated instances of arrhythmias, such as supravascular extrasystole, arterial fibrillation and left bundle branch block have been reported during chronic flupirtine therapy.

- **HEPATOTOXICITY:**

Elevated liver enzymes, Deterioration of hepatic functions in patients with preexisting liver disease has been noted.

- **NEPHROTOXICITY:**

Elevation in blood urea nitrogen and serum creatinine have been observed.

- **CNS SIDE EFFECTS:**

Anxiety, Depression, Dizziness, Fatigue, Hallucination, Headache,Insomnia, Weakness, Tremors.

# LITERATURE REVIEW

- **Heusinger JH** et al conducted a study with 1174 patients with pain due to various causes. Treatment was given, depending on the indication, for between 3 days and 8 weeks. For both drugs rectal as well as oral medication was used. It is stated that Flupirtine proved to be at least as efficacious as pentazocine and was better tolerated producing about half as many adverse reactions and about one third of the drop out rate.
- **Colin S. Goodchild** et al published "Combination Therapy with Flupirtine and Opioid: Open-Label Case Series in the Treatment of Neuropathic Pain Associated with Cancer" in this Ten patients were recruited. Only one patient was withdrawn because of side effects. Several pain measurements were used. There were significant reductions of average pain ($P < 0.01$) and neuropathic pain discriminant scores ($P < 0.01$), as well as an increase in percentage pain relief ($P < 0.01$). Eight patients elected to continue to take flupirtine after the trial, two taking 200 mg QID and the others 100 mg QID. Of these eight, six said that flupirtine was of considerable help and two said it helped a little.. This short duration open-label study in 10 subjects suggests that flupirtine may be useful in the treatment of neuropathic pain when used in combination with opioids.
- **Sanja Perovic** et al published " Flupirtine increases the levels of glutathione and Bcl-2 in hNT neurons: mode of action of the drug-mediated anti-apoptotic effect" in this study hNT neurons were induced to apoptosis applying glutamate (Glu; at concentrations > or = 1 mM) or NMDA (> or = 1 mM). During Glu/NMDA-mediated apoptosis the levels of the intracellular anti-apoptotic agents Bc1-2 and glutathione dropped by more than 50%. Flupirtine completely abolished this reduction of Bc1-

2 and glutathione level at a concentration of 10 microM. In the presence of 3 microM flupirtine a > 6-fold increase of the Bc1-2 (B-cell leukemia/lymphoma-2) level was observed in hNT neurons. stated that the View the MathML source neuronal cell death in vitro is controlled at least partially by Bcl-2 and glutathione. Neuronal cell death by Glu or NMDA in vitro can be overcome applying the drug flupirtine which is in clinical use.

- **Lia.C** et al published "Analgesic efficacy and tolerability of flupirtine vs. tramadol in patients with subacute low back pain: a double-blind multicentre trial" in this randomised, double-blind, parallel-group trial, 209 LBP patients, aged 18-65 years, were orally treated with flupirtine 100 mg (n = 105) vs. tramadol 50 mg (n = 104), both three times daily for 5-7 day stated Flupirtine 100 mg three times daily was associated with a reduction in pain and improvements in functional capacity equivalent to that observed with tramadol 50 mg three times daily, and was better tolerated.
- **Jae C. Chang** et al published "Utility of naproxen in the differential diagnosis of fever of undetermined origin in patients with cancer" in this study Twenty-two patients with cancer and fever of undetermined origin for more than seven days were treated with naproxen to control fever when there was no evidence of infection after a careful initial evaluation, and in most cases, after failure of antibiotic therapy. In final analysis, none of five patients with infectious fever had responses to naproxen. In contrast, 14 of 15 patients with neoplastic fever showed a prompt, complete, and sustained lysis of fever within 24 hours after the initiation of naproxen treatment, and the patients also showed symptomatic improvement. stated data suggest that naproxen specifically produces the lysis of neoplastic fever and, therefore, is a useful agent in assisting in the

differential diagnosis of infectious fever and neoplastic fever in patients with cancer and fever of undetermined origin.

- **Richard O Day** et al published "Relationship of serum naproxen concentration to efficacy in rheumatoid arthritis " in this study Twenty-four patients with rheumatoid arthritis were tested in a randomized, double-blind. Latin-square comparison of 250, 750 and 1500 mg of naproxen daily. Each received each dose for 2 wk and baseline disease activity was established during withdrawal of medication before and after the study. stated Patients with a trough total serum naproxen concentration under 18 microg/ml did not respond, while 76% of patients with trough total serum concentrations above 50 microg/ml responded. No serum naproxen toxicity level relationship was established.
- **TSAVARIS.N** et al published "A randomized trial of the effect of three non-steroid antiinflammatory agents in ameliorating cancer-induced fever" in this study randomized 48 patients to receive three different non-steroid anti-inflammatory drugs: Naproxen (500 mg d-1), Indomethacin (75 mg d-1) or Diclophenac sodium (75 mg d-1). All patients had solid tumours, and microbial infection had been excluded. All three drugs were equally effective in bringing the temperature down to normal for a period of 30-33 d. stated that Naproxen, Indomethacin and Diclophenac sodium are equally effective in ameliorating paraneoplastic fever. In relapse, a second drug given subsequently can be effective as well.
- **Vernon E** et al published "Chemopreventive Efficacy of Naproxen and Nitric Oxide–naproxen in Rodent Models of Colon, Urinary Bladder, and Mammary Cancers" in this study naproxen administered at 200 and 400 ppm in the diet reduced mean ACFs in the colon by about 45% to 60%, respectively. NO-naproxen was likewise administered in the diet at roughly equimolar doses (300 and 600 ppm) and reduced total ACF by

20% to 40%, respectively. In the hydroxybutyl (butyl) nitrosamine rat urinary bladder cancer model, NO-naproxen was given at 183 or 550 ppm in the diet, and naproxen at 128 ppm. The NO-naproxen groups had 77% and 73% decreases, respectively, in the development of large urinary bladder tumors, whereas the 128 ppm naproxen group also showed a strong decrease (69%). If treatments were started 3 months after hydroxybutyl (butyl) nitrosamine, NO-naproxen (550 ppm) and naproxen (400 ppm) were also highly effective (86-94% decreases). In the methylnitrosourea-induced mammary cancer model in rats, NO-naproxen and naproxen showed nonsignificant inhibitions (12% and 24%) at 550 and 400 ppm, respectively. stated that both naproxen and NO-naproxen are effective agents against urinary bladder and colon, but not mammary, carcinogenesis.

- **Sandy Srinivas** et al plublished "A Phase II Trial of Calcitriol and Naproxen in Recurrent Prostate Cancer" in this study Twenty-one patients were enrolled in the trial. Four patients met criteria for progression, with a PSA doubling time (PSADT) that decreased while on therapy. Fourteen patients had a prolongation of PSADT compared to baseline. This study stated Combination therapy with weekly calcitriol and daily naproxen is well tolerated by most patients and prolongation of PSADT was achieved in 75% of patients.
- **Harish S** et al published "Flupirtine: Clinical pharmacology" this Study have shown that flupirtine reduced cancer pain more effectively than tramadol and pentazocine. Also, the adverse reaction profile was similar in both flupirtine and tramadol treated patients. But, with an increased incidence of central nervous system (CNS) side effects to pentazocine when compared with flupirtine which concluded Studies suggest flupirtine as an effective analgesic for treatment of acute pain states such

as postoperative pain, traumatic injury, headache, and migraine, as well as chronic pain such as musculoskeletal pain. It is effective and better tolerated for treatment of cancer pain.

- **Anton Kolosov** et al published "Flupirtine Enhances the Anti-Hyperalgesic Effects of Morphine in a Rat Model of Prostate Bone Metastasis" in this study Syngeneic prostate cancer cells were injected into the right tibia of male Wistar rats under anesthesia. This led to expanding tumor within the bone in 2 weeks, together with the concurrent development of hyperalgesia to noxious heat. Paw withdrawal thresholds from noxious heat were measured before and after the maximum non-sedating doses of morphine and flupirtine given alone and in combinations which concluded The results suggest that flupirtine in combination with morphine may be useful clinically to provide better analgesia at lower morphine doses in the management of pain caused by tumors growing in bone.
- **Jacques Devulder** et al published "Flupirtine in Pain Management" this study says Flupirtine displays indirect NDMA receptor antagonism via activation of potassium channels and is the first representative of a pharmacological class denoted the 'selective neuronal potassium channel openers'. The generation of the M-current is facilitated by flupirtine via the opening of neuronal Kv7 potassium channels.Neuronal hyperexcitability is a physiological component of many pain states such as chronic pain, migraine and neurogenic pain which concluded Flupirtine is an analgesic with many potential therapeutic benefits that may prove useful in the treatment of many disease states

- **Elango Panchanathan** et al published "Effect of flupirtine on the growth and viability of U373 malignant glioma cells" this study says Variations

in the growth of U373 MG cells in 5 mM N-methyl-D-aspartate (NMDA), 1 mM flupirtine, and combined treatment indicated the antagonistic effects of NMDA and flupirtine on MG cell lines. The variation in the percentage of gated cell population in different cell cycle phases showed significant variations after 48 h of treatment. which concluded A previous study compared the analgesic efficacy and safety of flupirtine with those of pentazocine; the results showed that flupirtine is significantly more effective and elicits fewer side effects than pentazocine when these two drugs are used to reduce very severe cancer-induced pain

- **Seema Mishra** et al published "Successful Use of Flupirtine in Refractory Neuropathic Pain Due to Small Fiber Neuropathy" in this study the case of a 22-year-old postoperative case of right frontoparietal oligodendroglioma who received multiple drugs for his severe neuropathic pain without significant relief were taken which concluded the pain almost completely subsided once flupirtine was added and substituted for some of the currently recommended first-line drugs.
- **Manasi Banerjee** et al published "Comparative study of efficacy and tolerability of flupirtine versus tramadol in non-steroidal anti-inflammatory drug intolerant mechanical low back pain" in this study randomized, single-blinded, intention to treat (ITT) trial started with 240 non-steroidal anti-inflammatory drug (NSAID) intolerant patients who were prescribed either tablet flupirtine (100 mg twice daily) or capsule tramadol (50 mg twice daily), for 4 weeks. Follow-up was done on days 14, 28 and 4 weeks after treatment completion. which concluded Flupirtine has better sustained efficacy and tolerability than tramadol .
- **Hoock** et al published "Crystalline form of flupirtine ((2-amino-6-(4-fluoro-benzylamino)-pyridin-3-yl)-carbamic acid ethyl ester)" in this The invention relates to novel multicomponent crystals, to the production

thereof, and to the use thereof for treating pain conditions, in particular of unclear genesis, by means of a simultaneous effect on pains which are caused by muscle tension or degenerative joint diseases as well as on pains that are based on inflammatory processes which concluded it is a centrally acting non-opioid analgesic which is devoid of the typical side effects of natural or synthetic opioids.

- **Bergmann JF** et al published "A randomised clinical trial of the effect of informed consent on the analgesic activity of placebo and naproxen in cancer pain" this is a randomized study in which Forty-nine patients with mild or moderate cancer pain which did not need narcotic analgesics entered the study. Twenty-five received both treatments without any information and constituted the uninformed group. Twenty-four had a complete information about the trial; six refused to participate. The 18 others constituted the informed-consent group. Visual analogue scales of pain before and 30, 60, 120 and 180 min after the intake of naproxen and placebo were recorded. this concluded that, in contrast with parallel studies, giving information in a crossover, placebo-controlled trial may increase the apparent efficacy of both the tested agent and the placebo, and decrease the perceived difference the two.
- **Stanley Levick** et al published "Naproxen sodium in treatment of bone pain due to metastatic cancer"this is a randomized, parallel study compared the efficacy and safety of two dosages of naproxen sodium (NS) in 100 patients with bone pain due to metastatic cancer. Patients were asked to rate their pain on a scale of 0–99; those patients with pain scores of 40 or more (indicating moderate to severe pain) were enrolled which concluded During use of NS, pain intensity scores decreased by approximately one-third in each treatment group.
- **Ventafridda** et al published "Sodium naproxen versus sodium diclofenac

in cancer pain control" this is a single-blind random study, simultaneously carried out by five Pain Therapy and Palliative Care Centres, the analgesic power and side-effects of sodium naproxen (CAS 26159-34-2) and sodium diclofenac (CAS 15307-86-5) by mouth were compared in a group of 100 advanced cancer patients which concluded that the similar analgesic effect of the two drugs--pain intensity and duration decreased by half in the first week of treatment--and a comparatively low morbidity rate.

- **Gallucci M** et al published "Nimesulide in the treatment of advanced cancer pain. Double-blind comparison with naproxen." This Is a clinical double-blind study, the analgesic efficacy and the side-effects of nimesulide (Aulin, CAS 51803-78-2) and naproxen administered to 68 patients affected by advanced cancer pain were compared. Patients were treated with non-steroidal anti-inflammatory drugs according to the first step of the pharmacological analgesic scale of the WHO. This is concluded drugs resulted to be effective with a low incidence of adverse events that may be related to their use.
- **Ronald A. Lubet** et al published "Screening Agents for Preventive Efficacy in a Bladder Cancer Model: Study Design, End Points, and Gefitinib and Naproxen Efficacy" in this study low and high dose aspirin altered the formation of large bladder tumors by 87% (decreased), 90% (decreased), 3% (increased), 6% (decreased) and 60% (decreased), respectively. Using protocol 2 Iressa and naproxen were also highly effective. Protocol 3 evaluation revealed that only Iressa caused a significant decrease in microscopic bladder cancers (63%). This concluded an established cancer end point appears preferable. Naproxen, which has an excellent cardiovascular profile, or epidermal growth factor receptor inhibitors may be effective in an adjuvant setting.

- **Stefan Grond** et al published "Assessment and treatment of neuropathic cancer pain following WHO guidelines"in this study The present study surveys 593 cancer patients treated by a pain service following the WHO guidelines for relief of cancer pain. Of these, 380 presented with nociceptive, 32 with neuropathic and 181 with mixed (nociceptive and neuropathic) pain. In patients with nociceptive, mixed and neuropathic pain, the average duration of evaluated pain treatment was 51, 53 and 38 days, respectively. which concluded that neuropathic cancer pain is not intractable and can be relieved in the majority of patients using analgesics.
- **Ewan Mc Nicol** et al published "Nonsteroidal Anti-Inflammatory Drugs, Alone or Combined With Opioids, for Cancer Pain" in this study Forty-two trials involving 3,084 patients met inclusion criteria: eight compared NSAID with placebo; 13 compared one NSAID with another; 23 compared NSAID with opioid, NSAID or opioid versus NSAID plus opioid combinations, or NSAID plus opioid combinations versus NSAID plus opioid combinations; and nine studies assessed the effect of increasing NSAID dose. This concluded studies demonstrated increased efficacy with increased NSAID dose, without dose-dependent increases in side effects.
- **Motsch.J** et al published "α-Adrenergic Agonists in Pain Therapy" this study is to investigate whether the stimulation of beta(2)-ARs could in fact be adequate to alleviateneuropathic allodynia. Neuropathy was induced in mice by sciatic nerve cuffing. We demonstrate that chronic but not acute stimulation of beta(2)-ARs with agonists such as clenbuterol, formoterol, metaproterenol and procaterol suppressed neuropathic allodynia. This concluded α-Adrenergic agonists such as flupirtine have recently become of interest to pain therapists and anesthesiologists, since

drugs of this class exhibit analgesic, sedative, anesthetic-sparing, and hemodynamic-stabilizing properties.

- **Mercadante.S** et al published "The use of anti-inflammatory drugs in cancer pain" this study says The role of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer pain has been well established in the treatment of mild pain and also alone or in association with opioids for the treatment of moderate to severe pain. Acutely, NSAIDs may be more than mild analgesics, and may provide additional analgesia when combined with opioids.this concluded The role of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer pain has been well established in the treatment of mild pain and also alone or in association with opioids for the treatment of moderate to severe pain.
- **Martino G** et al published "A controlled study of the analgetic effect of two non-steroidal anti-inflammatory drugs in cancer pain." this is double-blind cross-over trial was carried out in 18 patients of both sexes suffering from pain due to malignant tumours who received single doses of 200 mg indoprofen and 250 mg naproxen p.o. Both compounds were efficacious and there was no difference in the duration of their activity in spite of the great difference between their half-lives.**Boris Zernikow** et al published "Paediatric cancer pain management using the WHO analgesic ladder results of a prospective analysis from 2265 treatment days during a quality improvement study" this study says Two hundred and twenty four patients (median age, 9 years; range 0.2-32.1) were enrolled. Three hundred and thirty three pain episodes comprising a total of 2265 treatment days were documented which concluded there is no evidence that a combination of an opioid with a non-opioid is more effective than opioid therapy alone in in-patient paediatric oncology pain treatment.
- **Rianne de Wit** et al published "The Treatment of Chronic Cancer Pain in

a Cancer Hospital in the Netherlands" this is a prospective study of 313 Dutch cancer patients with chronic pain, the practice of pain treatment was evaluated by means of Donabedian's structure-process-outcome framework. The practice of pain treatment concluded that After discharge, only 36.8% of the district nurses were informed about patients' pain. These results emphasize that continuing efforts to improve the practice of pain treatments are needed.

- **Goodchild C** et al published "Synergistic Interactions Between a KCNQ Channel Opener and an Opioid: Flupirtine and Morphine in Rat Pain Models Including Neuropathic Pain" Experiments were performed in rats in an observer blinded fashion with vehicle controls. which concluded Flupirtine should be investigated as an adjunct analgesic with opioids for the management of patients with severe pain states.

# AIM and OBJECTIVE:

**AIM:**

The aim of this study is to compare the efficacy and safety of Naproxen and Flupiritin in cancer patients.

**OBJECTIVES:**

- To measure the pain intensity in cancer patients
- To compare the effectiveness and safety of pain therapies in cancer patients using pain rating scales.
- To monitor the adverse drug reactions and their management in cancer patients.

# PLAN OF WORK:

The entire study was carried out for a period of nine months from june 2013 to feb 2014 in Meenakshi mission hospital and research centre, Madurai. The proposal was designed as given below.

June - July 2013

- Literature survey.
- Obtaining consent from the hospital authority.
- Study design including design of data entry form.

August - December 2013

- Selection of patients
- Obtaining consent from patients.
- Collection of patient detail
- Collection of lab datas

January - February 2014

- Compilation.
- statistical analysis
- Submission of reports.

# METHODOLOGY

## SITE OF THE STUDY:

The study was carried out in Meenakshi mission hospital and research centre, Madurai from july 2012 onwards. The hospital is unique and well known for its service to people who come from all over the southern district and various parts of the state.

Department selected for study in the Hospital:

Both inpatients and outpatients from the Oncology departments.

## PATIENT SELECTION:

### Inclusion criteria:

- Patients of both genders and aged above 20 years having

  - pain related to cancer

- And only those patients who are willing to give consent.

### Exclusion criteria:

- Pregnant and lactating women
- Previous history of allergy to Flupirtine / Naproxen.
- Non solid tumors
- Patients with conditions like renal failure.

**STUDY GROUPS:**

Patients grouped into two categories

Group A

Group B

- Group A = Cancer patients received Flupirtine.
- Group B = Cancer patients received Naproxen .

Patients Enrollment = 30 (A) + 30 (B) =60

**STUDY DESIGN:**

DESIGN OF DATA ENTRY FORMAT (PROFORMA)

- A separate data entry format [proforma] for incorporating patient's details was designed. The format contains details as follows.

Proforma I

- Patients informed consent form.

Proforma II

- Patient details.

Proforma III

- Pain Rating Scale

Proforma IV

- Adverse Reaction Monitoring.

Proforma V

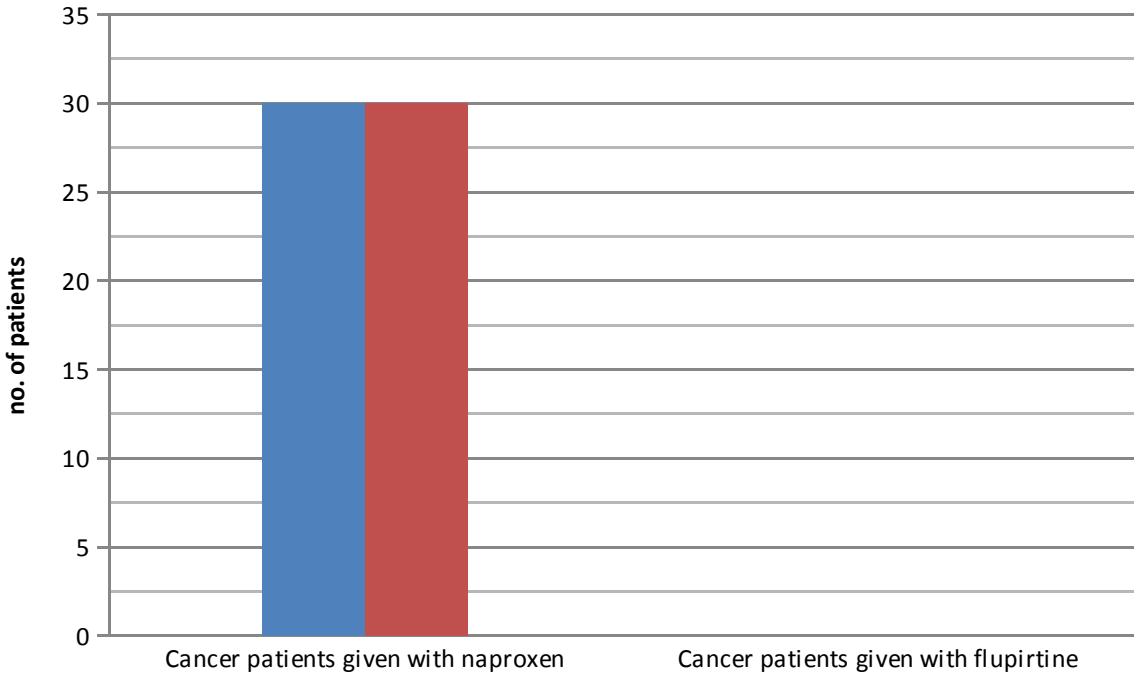
- Patient satisfaction scale report.

# OBSERVATION AND RESULTS:

## POPULATION AMONG THE GROUP:

| S.NO S | GROUPS | NO.OF PATIENTS | PERCENTAGE % |
|---|---|---|---|
| 1 | Cancer patients given with Naproxen | 30 | 50 |
| 2 2 | Cancer patients given with Flupirtine | 30 | 50 |
| 3 | Total | 60 | 100 |

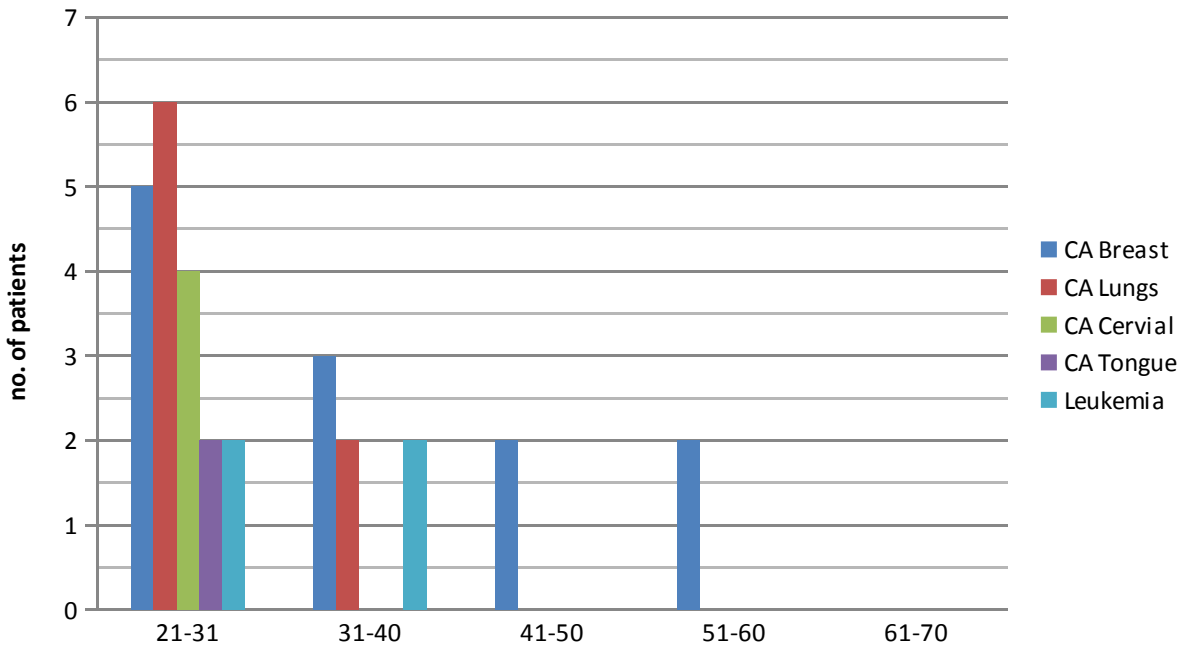
Table no. 1




## AGE WISE DISTRIBUTION GROUP (A): `

| TYPES OF CANCER | | | | | | |
|---|---|---|---|---|---|---|
| **AGE** | **BREAST CANCER** | **LUNG CANCER** | **CERVICAL CANCER** | **TONGUE CANCER** | **LEUKEMIA** | **TOTAL** |
| 21 – 30 | | | 4 | | 2 | 6 |
| 31 - 40 | 5 | | | | | 5 |
| 41 – 50 | 3 | | | | 2 | 11 |
| 51 – 60 | 2 | 6 | | | | 4 |
| 61 – 70 | 2 | 2 | | 2 | | 4 |
| | | | | TOTAL | | 30 |

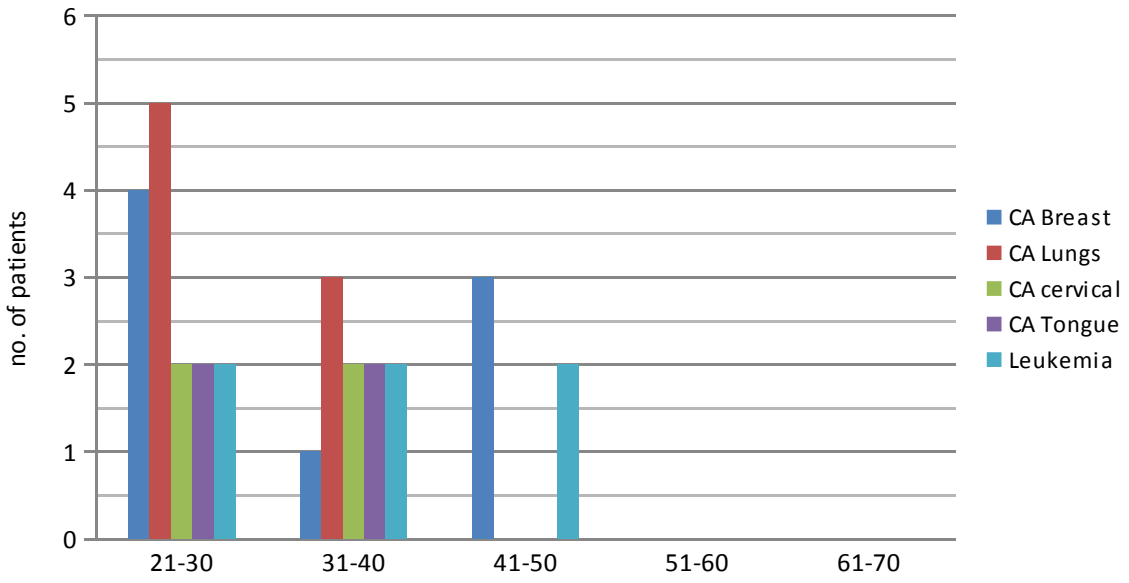
Table 2




## AGE WISE DISTRIBUTION GROUP (B):

| TYPES OF CANCER | | | | | | |
|---|---|---|---|---|---|---|
| **AGE IN YEARS** | **BREAST CANCER** | **LUNG CANCER** | **CERVICAL CANCER** | **TONGUE CANCER** | **LEUKEMIA** | **TOTAL** |
| 21 - 30 | | | 2 | | 2 | 4 |
| 31 - 40 | | 5 | | | | 5 |
| 41 – 50 | 4 | | | | 2 | 6 |
| 51 - 60 | 1 | 3 | 2 | 2 | | 8 |
| 61 - 70 | 3 | | | 2 | 2 | 7 |
| | | | | TOTAL | | 30 |

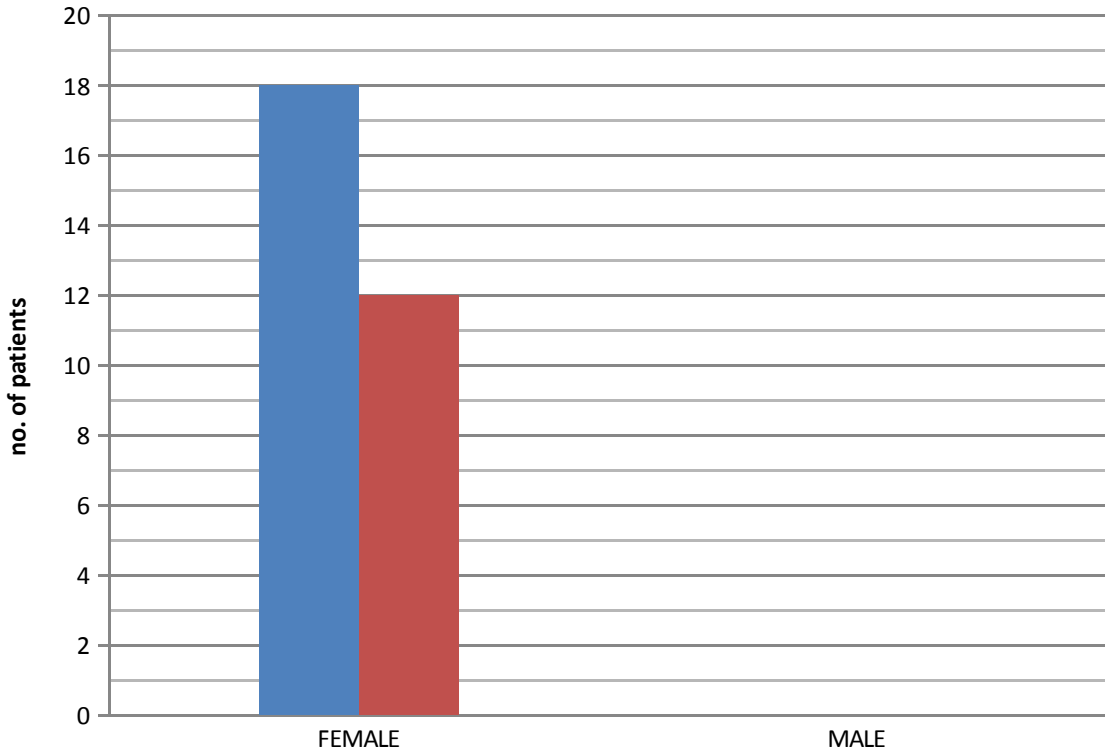
Table 3



## GENDER WISE DISTRIBUTION GROUP (A):

| S.NO | GENDER | NO. OF PATIENTS | PERCENTAGE % |
|---|---|---|---|
| 1 | FEMALE | 18 | 60 |
| 2 | MALE | 12 | 40 |

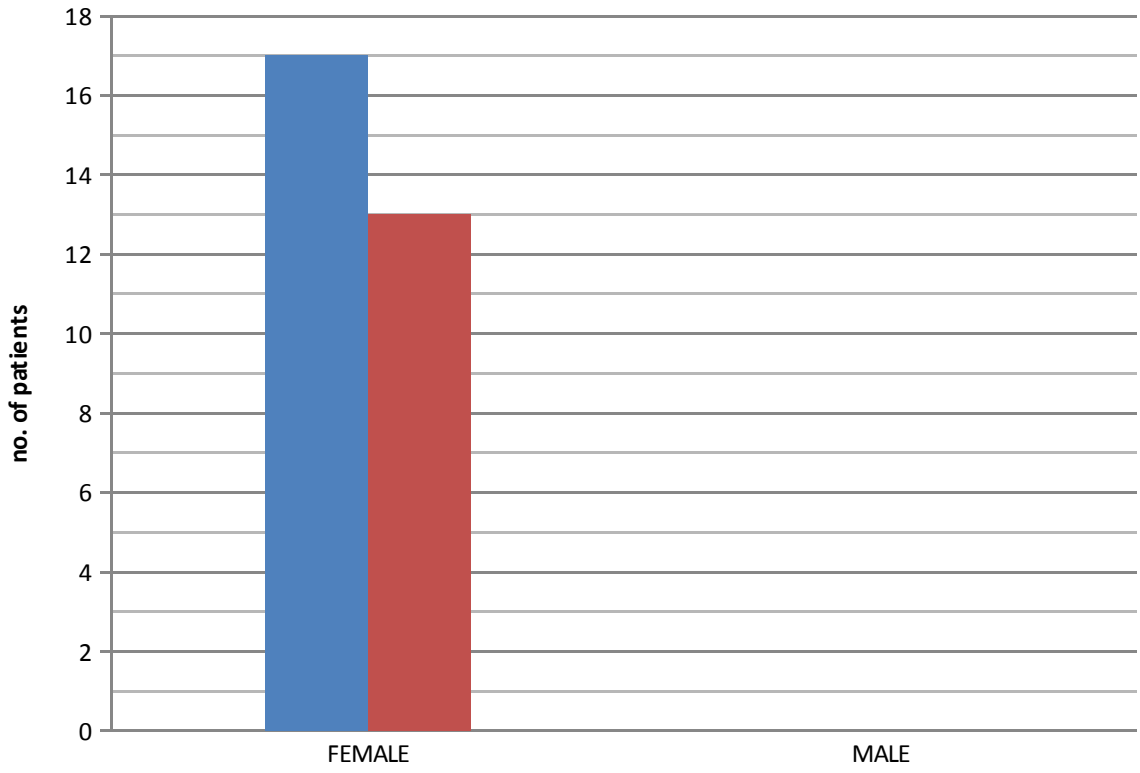
Table 4




## GENDER WISE DISTRIBUTION GROUP (B):

| S.NO | GENDER | NO. OF PATIENTS | PERCENTAGE % |
|---|---|---|---|
| 1 | FEMALE | 17 | 56.6 |
| 2 | MALE | 13 | 43.3 |

Table 5

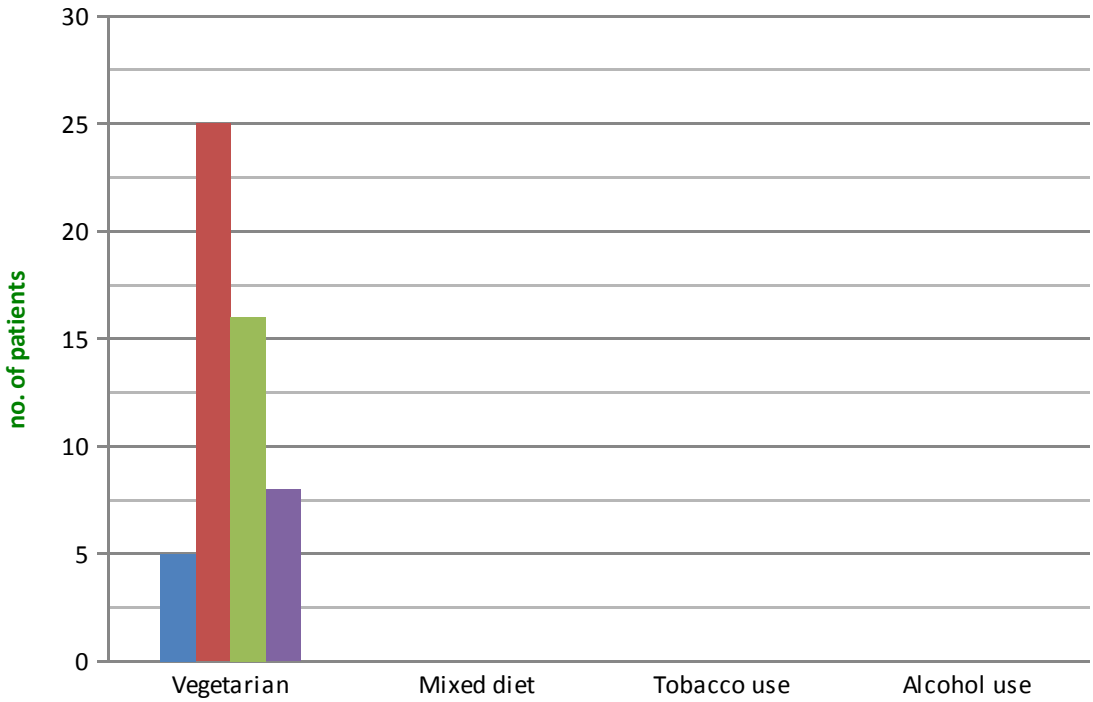



## SOCIAL HABITS:

GROUP (A)

| | |
|---|---|
| VEGETARIAN | 5 |
| MIXED DIET | 25 |
| TOBACCO USE | 16 |
| ALCOHOL USE | 6 |

Table 6

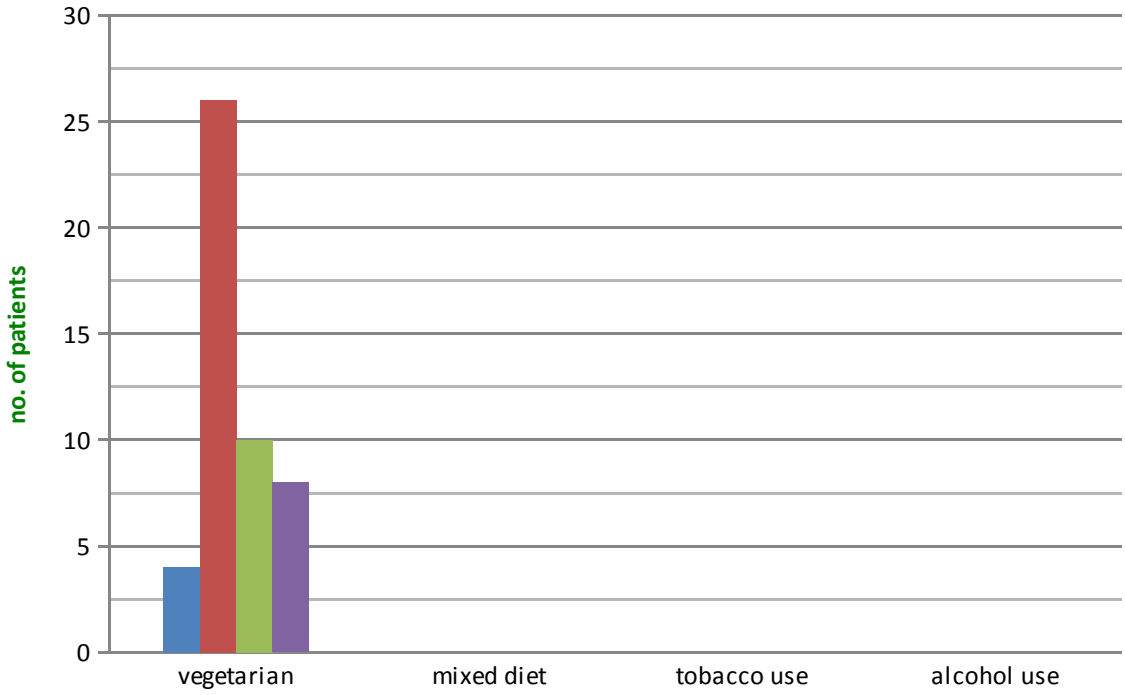



**SOCIAL HABITS**:

GROUP (B):

| | |
|---|---|
| VEGETARIAN | 4 |
| MIXED DIET | 26 |
| TOBACCO USE | 10 |
| ALCOHOL USE | 8 |

Table 7




## PARTS AFFECTED:

GROUP (A):

| S.NO | PARTS AFFECTED | NO. OF PATIENTS |
|---|---|---|
| 1 | BREAST | 12 |
| 2 | LUNG | 8 |
| 3 | CERVICAL | 4 |
| 4 | TONGUE | 2 |
| 5 | LEUKEMIA | 4 |

Table 8

## PARTS AFFECTED

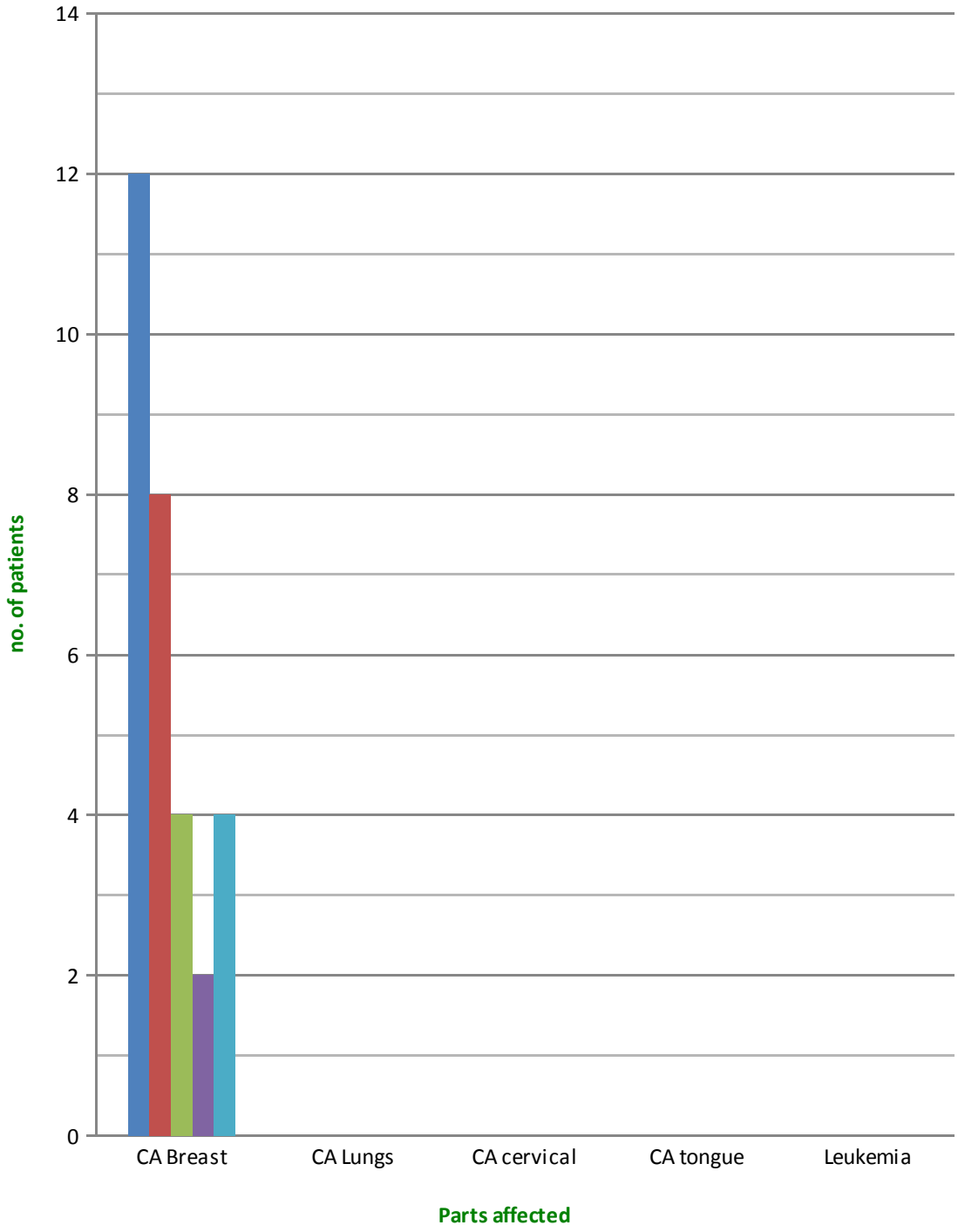
GROUP (B):

| S.NO | PARTS AFFECTED | NO. OF PATIENTS |
|---|---|---|
| 1 | BREAST | 8 |
| 2 | LUNGS | 8 |
| 3 | CERVICAL | 4 |
| 4 | TONGUE | 4 |
| 5 | LEUKEMIA | 6 |

Table 9:

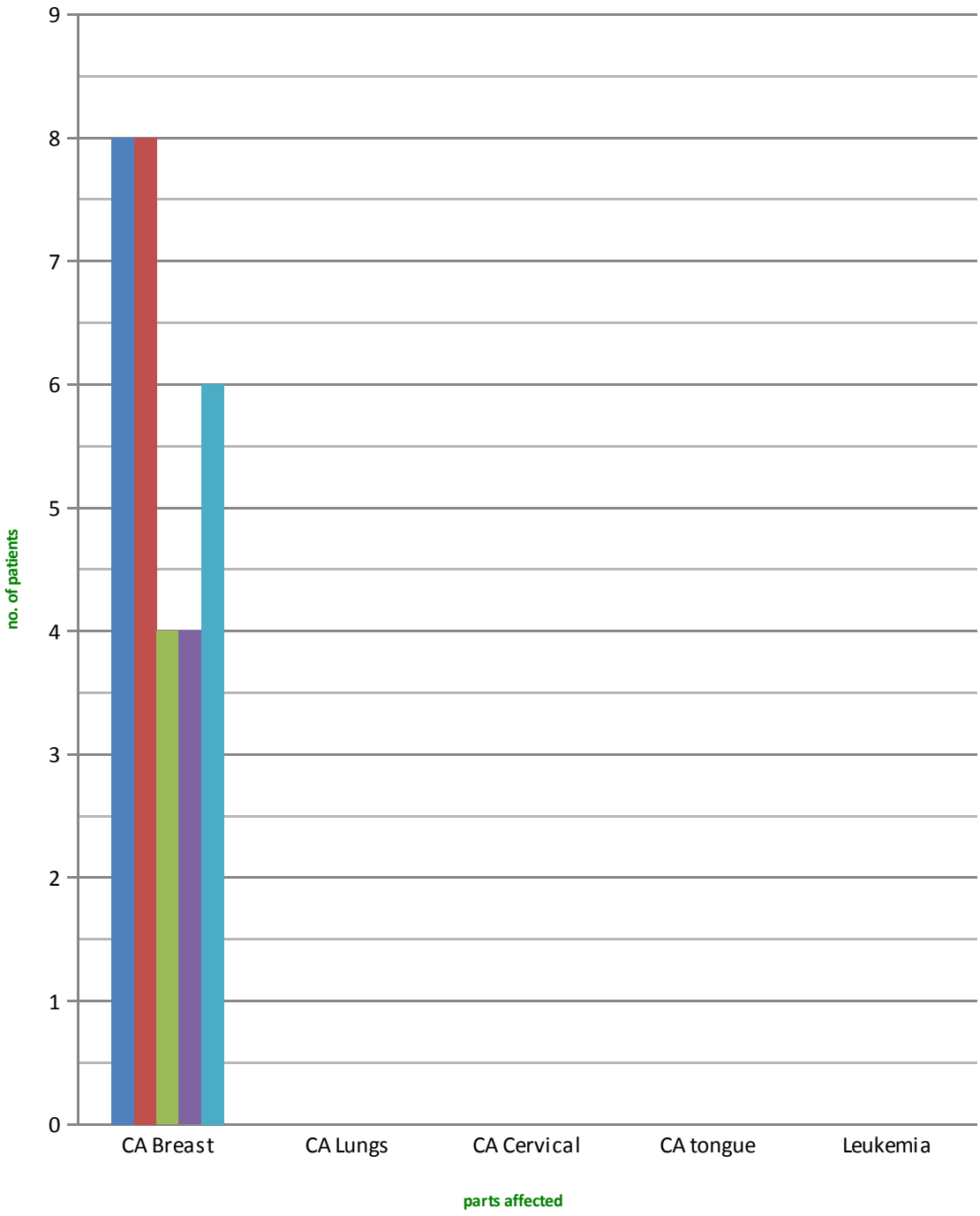
## PARTS AFFECTED:

GROUP (A):




**PARTS AFFECTED**

GROUP (B):




**PAIN RATING SCALE:** GROUP (A):

Pain rating scale:0 1 2 3 4 5 6 7 8 9 10

0-No pain, (1-3)-mild pain,(4-6)-moderate pain, (7-10)-severe pain.

Table 10:

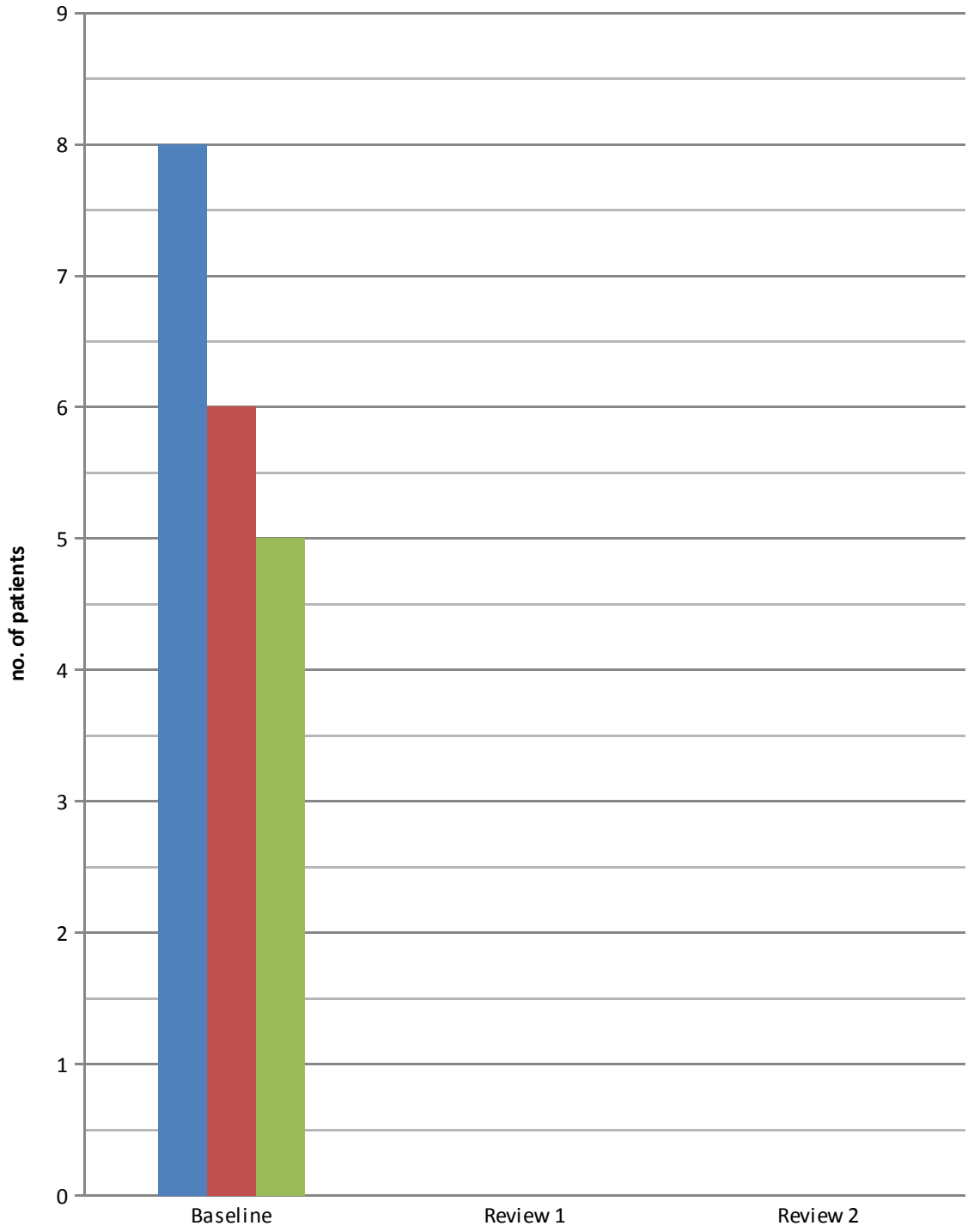
| S.No | Patient I.D | Baseline | Review 1 | Review 2 |
|---|---|---|---|---|
| 1 | A1 | 10 | 7 | 3 |
| 2 | A2 | 8 | 5 | 2 |
| 3 | A3 | 9 | 4 | 2 |
| 4 | A4 | 6 | 3 | 1 |
| 5 | A5 | 7 | 4 | 1 |
| 6 | A6 | 9 | 5 | 2 |
| 7 | A7 | 6 | 3 | 1 |
| 8 | A8 | 4 | 2 | 0 |
| 9 | A9 | 10 | 7 | 3 |
| 10 | A10 | 5 | 3 | 0 |
| 11 | A11 | 8 | 4 | 2 |
| 12 | A12 | 9 | 6 | 3 |
| 13 | A13 | 8 | 5 | 3 |
| 14 | A14 | 6 | 3 | 1 |
| 15 | A15 | 7 | 4 | 1 |
| 16 | A16 | 10 | 8 | 3 |

| | | | | |
|---|---|---|---|---|
| 17 | A17 | 8 | 5 | 2 |
| 18 | A18 | 9 | 5 | 2 |
| 19 | A19 | 7 | 3 | 1 |
| 20 | A20 | 8 | 5 | 2 |
| 21 | A21 | 8 | 4 | 1 |
| 22 | A21 | 5 | 2 | 0 |
| 23 | A23 | 8 | 5 | 2 |
| 24 | A24 | 5 | 3 | 0 |
| 25 | A25 | 6 | 3 | 1 |
| 26 | A26 | 10 | 7 | 3 |
| 27 | A27 | 9 | 6 | 3 |
| 28 | A28 | 6 | 3 | 1 |
| 29 | A29 | 10 | 6 | 2 |
| 30 | A30 | 9 | 5 | 3 |

Table 10

## MEAN PAIN INTENSITY SCORE:

Effect of naproxen in Group A :




**PAIN RATING SCALE:** GROUP (B):

Pain rating scale:0 1 2 3 4 5 6 7 8 9 10

0-No pain, (1-3)-mild pain,(4-6)-moderate pain, (7-10)-severe pain.

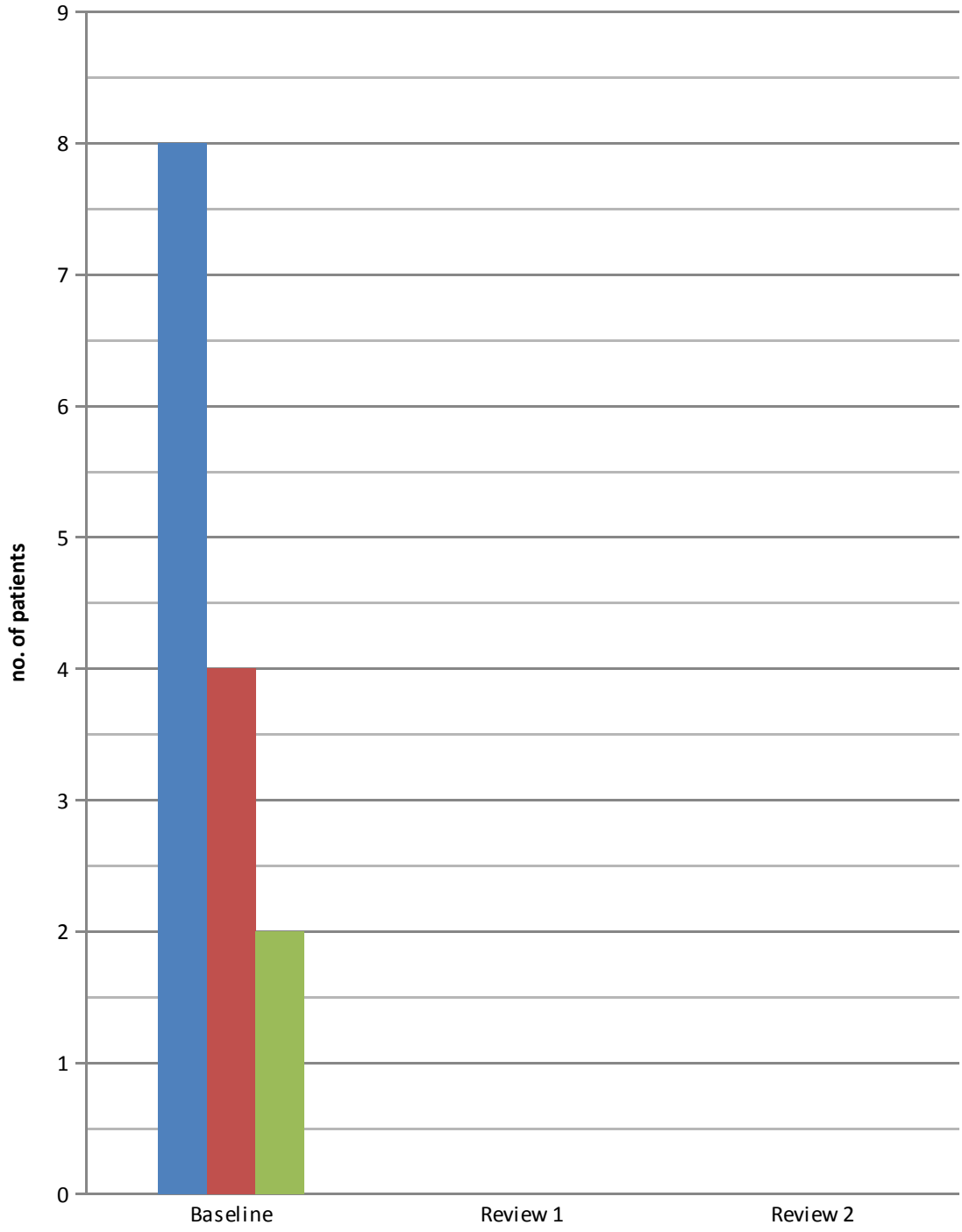
| S.No | Patient I.D | Baseline | Review 1 | Review 2 |
|---|---|---|---|---|
| 1 | B1 | 10 | 7 | 3 |
| 2 | B2 | 8 | 5 | 2 |
| 3 | B3 | 9 | 4 | 2 |
| 4 | B4 | 6 | 3 | 1 |
| 5 | B5 | 7 | 4 | 1 |
| 6 | B6 | 9 | 5 | 2 |
| 7 | B7 | 6 | 3 | 1 |
| 8 | B8 | 4 | 2 | 0 |
| 9 | B9 | 10 | 7 | 3 |
| 10 | B10 | 5 | 3 | 0 |
| 11 | B11 | 8 | 4 | 2 |
| 12 | B12 | 9 | 6 | 3 |
| 13 | B13 | 8 | 5 | 3 |
| 14 | B14 | 6 | 3 | 1 |
| 15 | B15 | 7 | 4 | 1 |
| 16 | B16 | 10 | 8 | 3 |

| | | | | |
|---|---|---|---|---|
| 17 | B17 | 8 | 5 | 2 |
| 18 | B18 | 9 | 5 | 2 |
| 19 | B19 | 7 | 3 | 1 |
| 20 | B20 | 8 | 5 | 2 |
| 21 | B21 | 8 | 4 | 1 |
| 22 | B21 | 5 | 2 | 0 |
| 23 | B23 | 8 | 5 | 2 |
| 24 | B24 | 5 | 3 | 0 |
| 25 | B25 | 6 | 3 | 1 |
| 26 | B26 | 10 | 7 | 3 |
| 27 | B27 | 9 | 6 | 3 |
| 28 | B28 | 6 | 3 | 1 |
| 29 | B29 | 10 | 6 | 2 |
| 30 | B30 | 9 | 5 | 3 |

Table 11

**MEAN PAIN INTENSITY SCORE**

Effect of in flupirtine Group B :



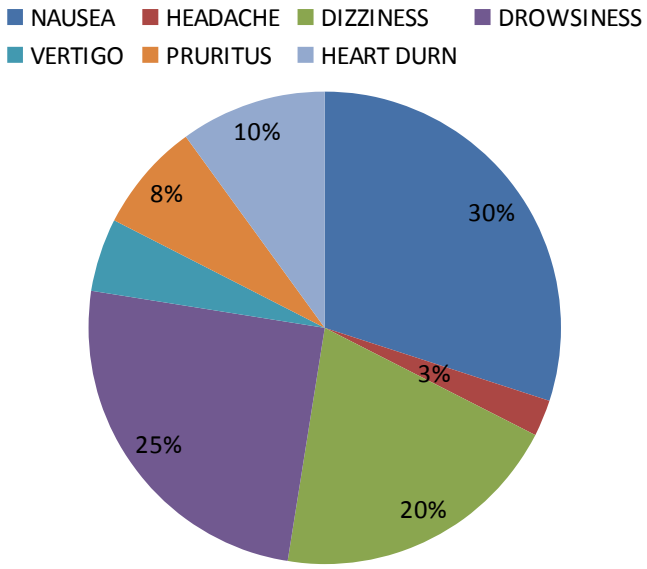
## ADVERSE REACTION MONITORING (GROUP A) :

| NO | Symptoms | Review I | Review II |
|---|---|---|---|
| 1 | Nausea | 12 | 10 |
| 2 | Headache | 1 | 2 |
| 3 | Dizziness | 8 | 7 |
| 4 | Drowsiness | 10 | 8 |
| 5 | Vertigo | 2 | 1 |
| 6 | Pruritus | 3 | 2 |
| 7 | Heart burn | 4 | 3 |

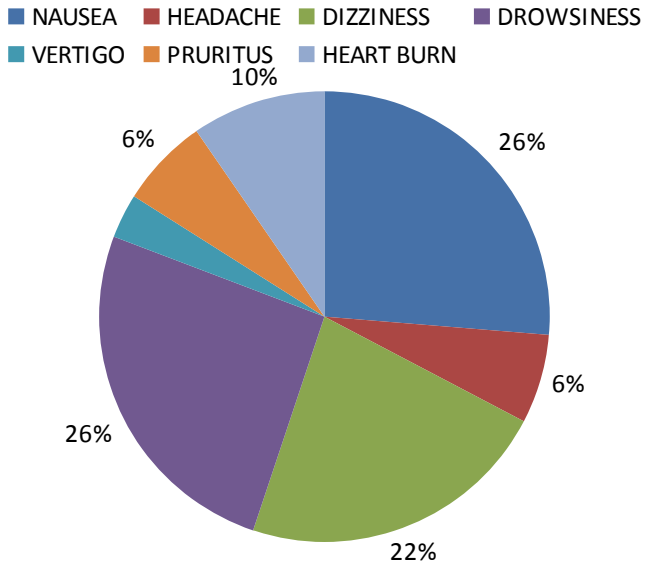
Table 12

## ADVERSE REACTION MONITORING (GROUP A) :

### REVIEW 1




### REVIEW 2



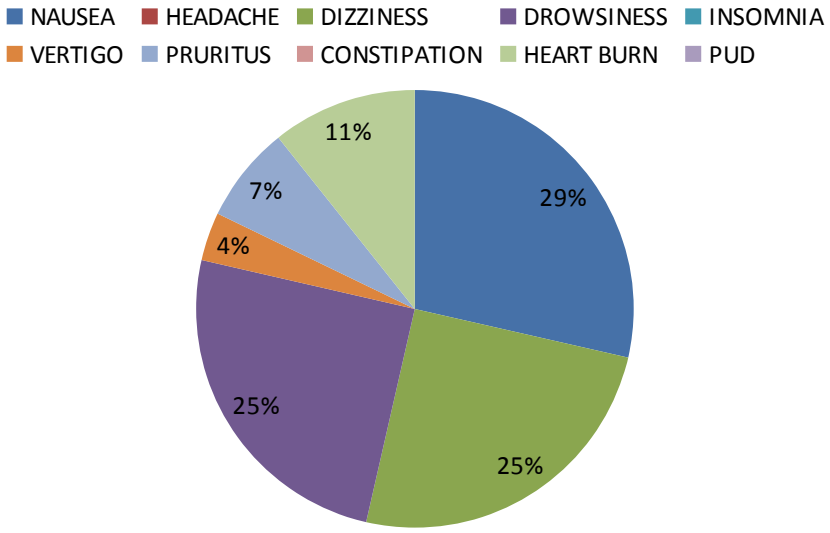
## ADVERSE REACTION MONITORING (GROUP B) :

| S.NO | Symptoms | Review I | Review II |
|---|---|---|---|
| 1 | Nausea | 10 | 8 |
| 2 | Headache | 2 | 0 |
| 3 | Dizziness | 6 | 7 |
| 4 | Drowsiness | 8 | 7 |
| 5 | Vertigo | 0 | 1 |
| 6 | Pruritus | 3 | 2 |
| 7 | Heart burn | 2 | 3 |

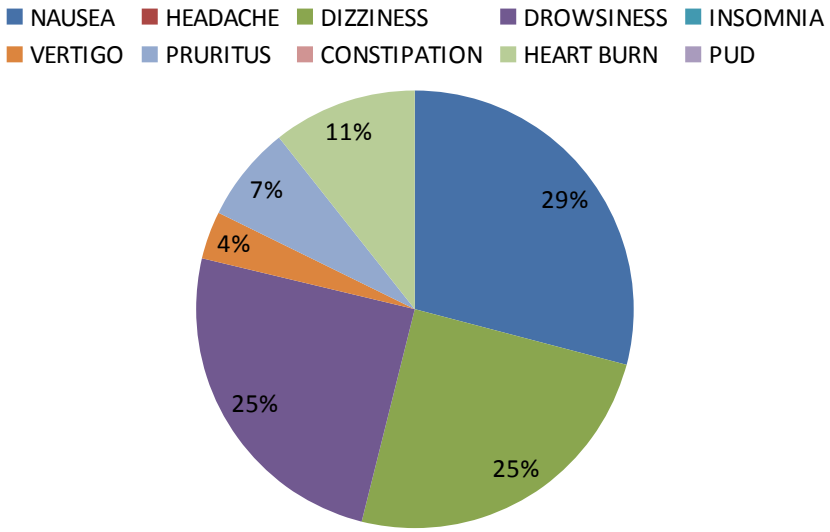
Table 13

## ADVERSE REACTION MONITORING (GROUP B) :

### REVIEW 1




### REVIEW 2



**PATIENT SATISFACTION SCALE GROUP "A"**

1 2 3 4 5

1-very satisfied , 2-Somewhat satisfied , 3-Neither satisfied nor dissatisfied
4-Somewhat dissatisfied , 5-Very dissatisfied.

| Serial no. | Patient ID | Review I | Review II |
|---|---|---|---|
| 1 | A1 | 1 | 1 |
| 2 | A2 | 2 | 1 |
| 3 | A3 | 4 | 3 |
| 4 | A4 | 2 | 1 |
| 5 | A5 | 5 | 5 |
| 6 | A6 | 5 | 5 |
| 7 | A7 | 1 | 1 |
| 8 | A8 | 2 | 2 |
| 9 | A9 | 4 | 3 |
| 10 | A10 | 3 | 2 |
| 11 | A11 | 5 | 5 |
| 12 | A12 | 5 | 4 |
| 13 | A13 | 4 | 4 |
| 14 | A14 | 4 | 4 |
| 15 | A15 | 4 | 3 |

| | | | |
|---|---|---|---|
| 16 | A16 | 4 | 3 |
| 17 | A17 | 4 | 4 |
| 18 | A18 | 3 | 2 |
| 19 | A19 | 5 | 4 |
| 20 | A20 | 5 | 4 |
| 21 | A21 | 3 | 1 |
| 22 | A22 | 4 | 3 |
| 23 | A23 | 3 | 2 |
| 24 | A24 | 4 | 3 |
| 25 | A25 | 5 | 5 |
| 26 | A26 | 3 | 3 |
| 27 | A27 | 3 | 2 |
| 28 | A28 | 4 | 4 |
| 29 | A29 | 5 | 5 |
| 30 | A30 | 4 | 3 |
| 31 | Mean± SD | 3.667±1.184 | 3.607±1.337*** |
| P value < 0.0001 ,*** very highly significant by paired t test | | | |

**PATIENT SATISFACTION SCALE GROUP "B"**

1 2 3 4 5

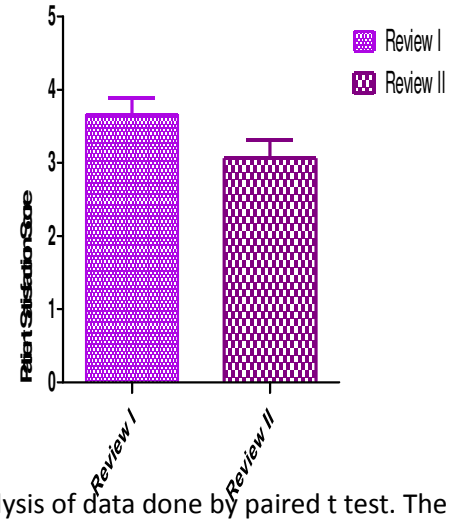
1-very satisfied , 2-Somewhat satisfied , 3-Neither satisfied nor dissatisfied
4-Somewhat dissatisfied , 5-Very dissatisfied.

| Serial no. | Patient ID | Review I | Review II |
|---|---|---|---|
| 1 | B1 | 2 | 2 |
| 2 | B2 | 2 | 2 |
| 3 | B3 | 1 | 1 |
| 4 | B4 | 1 | 1 |
| 5 | B5 | 2 | 1 |
| 6 | B6 | 3 | 2 |
| 7 | B7 | 1 | 1 |
| 8 | B8 | 1 | 1 |
| 9 | B9 | 3 | 2 |
| 10 | B10 | 2 | 1 |
| 11 | B11 | 2 | 1 |
| 12 | B12 | 1 | 1 |
| 13 | B13 | 3 | 2 |
| 14 | B14 | 2 | 1 |
| 15 | B15 | 5 | 5 |

| | | | |
|---|---|---|---|
| 16 | B16 | 2 | 1 |
| 17 | B17 | 2 | 2 |
| 18 | B18 | 2 | 1 |
| 19 | B19 | 2 | 1 |
| 20 | B20 | 2 | 2 |
| 21 | B21 | 3 | 1 |
| 22 | B22 | 2 | 2 |
| 23 | B23 | 5 | 4 |
| 24 | B24 | 3 | 2 |
| 26 | B26 | 3 | 1 |
| 25 | B25 | 2 | 1 |
| 27 | B26 | 3 | 1 |
| 28 | B28 | 3 | 2 |
| 29 | B29 | 2 | 1 |
| 30 | B30 | 1 | 1 |
| 31 | Mean ± SD | 2.533 ± 1.120 | 1.711 ± 1.160*** |
| P value < 0.0001 ,*** very highly significant by paired t test | | | |

# Mean Patient satisfaction scale report

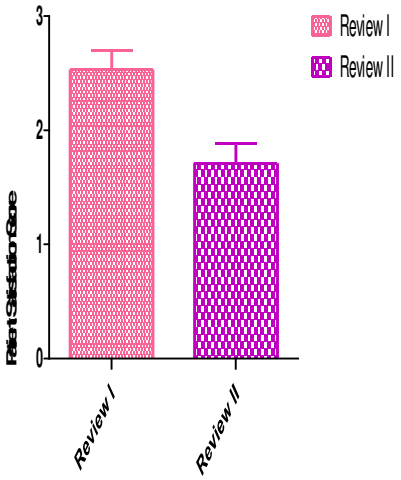
Group A




Data presented are mean ± SD analysis of data done by paired t test. The report shows very highly significant *** value for review II compared to review I.

# Mean Patient satisfaction scale report

Group B




Data presented are mean ± SD analysis of data done by paired t test. The report shows very highly significant *** value for review II compared to review I.

# DISCUSSION

## Demographic data:

In this study,

- Patients at the age of age between 51 - 60 are at increases risk for cancer
- CA lungs predominantly affect men than women.
- Major diagnosis in both group A and group B - CA breast

## Comparative data:

In Group A:

- Before therapy about 76% (n=23) of the patients were complained of severe pain
- About 24% (n=7) complained of moderate pain.

In patients with severe pain only 27% (n=6) of the patients were recovered by Naproxen and the remaining 73%(n=17) were not. But in the case of patients with moderate pain about 85% (n=12) of the patients were recovered by Naproxen therapy and only 15% (n=1) were not recovered.

In group B:

- Before therapy about 71 % (n=32) of the patients were complained of severe pain.
- About 29% (n=13) pf the patients were complained of moderate pain

In patients with severe pain about 82 % (n=26) of the patients were recovered by flupirtine therapy and only 18% (n=6) were not recovered. In patients with moderate pain about 98% (n=12) of the patients were recovered by flupirtine therapy and only 2% (n=1) were not recovered.

Moreover, in group A only 17% of the patients are satisfied with Naproxen therapy. But in group B about 60 % of the patients are very satisfied with flupirtine therapy.

**ADVERSE DRUG REACTION:**

- ✓ Major adverse drug reaction occurred in group A who received Naproxen and Group B who received flupirtine are dizziness, loss of appetite, nausea, vomiting etc.
- ✓ Nausea is more pronounced in cancer patients.
- ✓ None of the patients have complaint of PUD, and constipation or insomnia.

# CONCLUSION

From this study we clearly conclude that,

- Age 51-60 is at high risk of cancer.
- Lung cancer is more prevalent in men than in women.
- CA breast are more prevalent in women.
- According to the results, flupirtine is very effective and safety in the management of cancer pain compared to Naproxen.
- More number of patients are very satisfied with flupirtine in group B than Group A who were given with Naproxen.
- Adverse reactions are common in both the groups. Major adverse drug reactions occurred are dizziness, drowsiness, nausea, vomiting etc.
- The final conclusion of this study is that flupirtine is very effective and safe in the management of severe cancer pain compared to Naproxen.
- Naproxen is also effective and safe in the management of moderate pain in cancer patients.

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